5-HT_{1C} receptors and th ir therapeutic relevance

GA Kennett

SmithKline Beecham, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, UK

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Introduction

Considerable advances have been made in the understanding of 5-hydroxytryptamine (5-HT) receptor pharmacology in the last decade. In 1979 the existence of more than one 5-HT receptor binding site was recognised for the first time when [^{3}H]lysergic acid diethylamine (LSD) binding in the rat cortex was found to contain 5-HT and spiperone (Janssen, Figure 1) sensitive components [1]. The 5-HT sensitive component was described as 5-HT_1 and the spiperone sensitive portion 5-HT_2. Subsequently Pedigo *et al.* [2] showed that at least two 5-HT_1 receptors existed, since high affinity [^{3}H]5-HT binding was partially displaced by spiperone. These putative receptor subtypes were termed 5-HT_{1A} (spiperone sensitive) and 5-HT_{1B} and can be more specifically labeled by [^{3}H]8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT) [3,4] and [^{125}I]iodocyanopindolol [5] respectively. Subsequently 5-HT_{1C} [6] 5-HT_{1D} [7], 5-HT_{1E} [8], 5-HT_3 [9,10] and 5-HT_4 [11] receptors have been identified.

The 5-HT_{1C} receptor

5-HT_{1C} receptor binding studies

One area found to contain 5-HT_1 binding sites by autoradiographic studies was the rat choroid plexus [12]. However these '5-HT_1' receptors were found to bind [^{3}H]mesulergine (Sandoz, Figure 1), a putative 5-HT_2 receptor ligand [13], but not the 5-HT_2 specific ligand [^{3}H] ketanserin (Janssen, Figure 1) [14,15]. The 5-HT_{1A} ligand 8-OH-DPAT and 5-HT_{1B} ligand RU 24969 (Roussel UCLAF) also failed to displace [^{3}H]mesulergine binding from this site which was therefore termed the 5-HT_{1C} receptor [6]. The pharmacology of this receptor has a considerable similarity to that of the 5-HT_2 receptor. Thus most 'classical' 5-HT_2 receptor antagonists such as mianserin (Organon, Figure 1) and methysergide (Sandoz), are unable to discriminate between the two sites. Exceptions include ketanserin (Janssen, Figure 1), altanserin (Janssen), pirenperone (Janssen), and spiperone, all of which show selectivity for the 5-HT_2 receptor [16] as do two recently developed compounds RP 62203 (Rhone Poulenc, Figure 1) [17] and SR 46349B (Sanofi) [18] (Table 1). 5-HT_2 receptor agonists are also largely non-selective; indeed only a few compounds, whether agonist or antagonist, show selectivity for the 5-HT_{1C} over the 5-HT_2 site (Table 1). These include 1-methyl 5-HT (one hundred-fold selective), MK 212 (Merck Sharp & Dohme, Figure 2; fifty-fold selective), (+)3-(2-aminopropyl)benz[e]indole hydrochloride (thirty-three-fold selective) [19], 1-naphthyl piperazine (1-NP) (ten-fold selective), 1-(3-chlorophenyl) piperazine (mCPP, Figure 2; ten-fold selective) and LY 53857 (Lilly; six-fold selective). 5-HT_{1C} receptors have been pharmacologically characterized in pig and human choroid plexus tissue and rat cortex. There were only minor differences in the affinities of the thirteen compounds tested [20].

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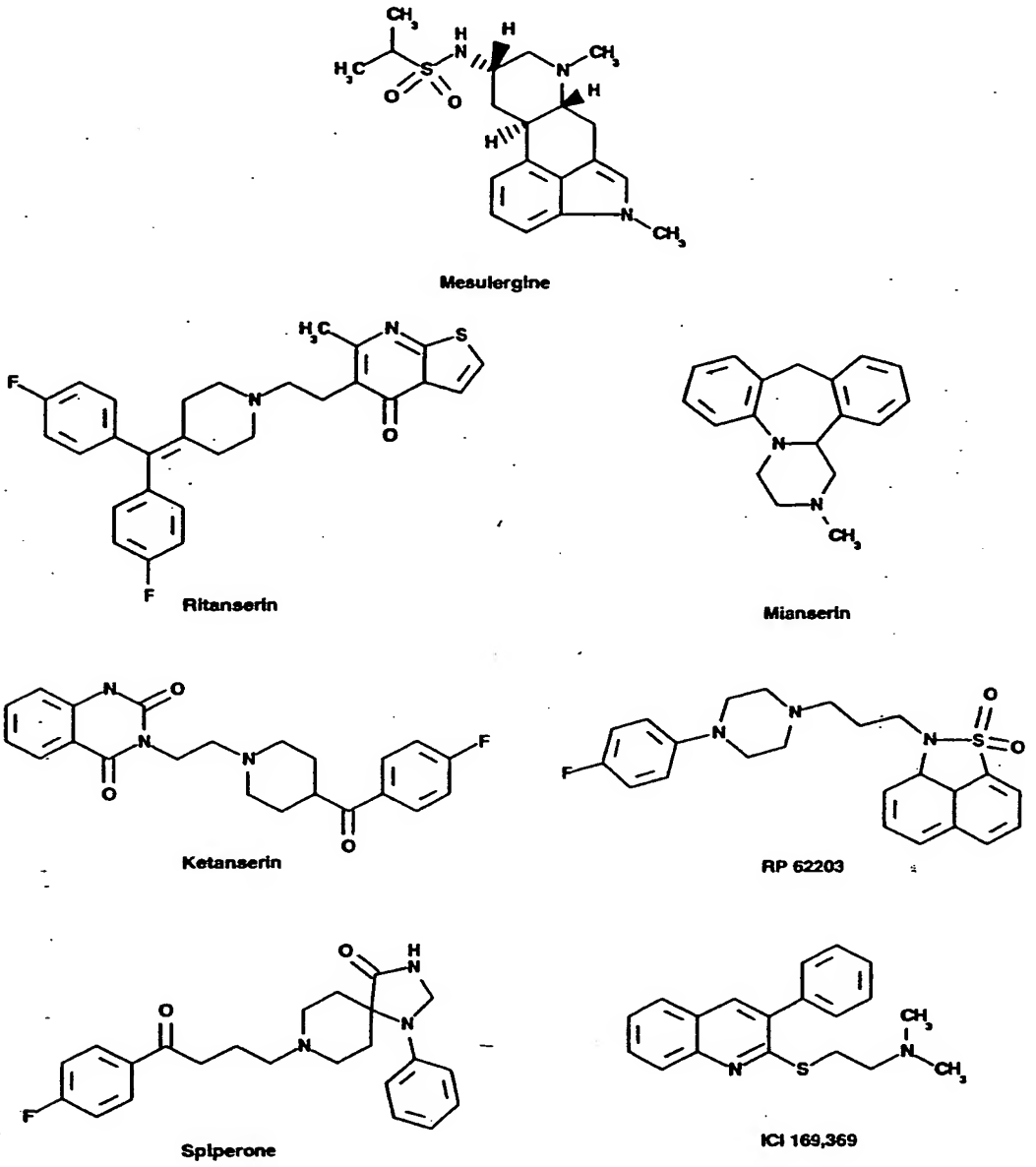


Figure 1: 5-HT_{1C}/5-HT_2 receptor antagonists

Several non-selective 5-HT_2/5-HT_{1C} receptor antagonists have been used clinically and many of the arguments advanced in the present review are based on their actions. Of these ICI 169,369 (Figure 1) and ICI 170,809 have the 'cleanest' profile. ICI 169,369 has thirteen-fold selectivity over the adrenergic α_1 receptor (Table 1). ICI 170,809 has twenty-fold higher affinity for 5-HT_{1C} site over the dopamine D_2 site and sixty-three-fold selectivity over the adrenergic α_1 receptor and one hundred-fold higher affinity for 5- HT_{1C} over the histamine H_1 site (Table 1). Ritanserin (Figure 1) has also been widely used clinically but has only three-fold selectivity for the 5-HT_{1C} over the H_1 receptor and only ten-fold over the adrenergic α_1 site. It also has high affinity for dopamine D_2 receptors (Table 1). Lastly mianserin is equipotent at 5-HT_{1C}, 5-HT_2 and H_1 receptors, has six-fold selectivity over 5-HT_3 and sixteen-fold selectivity over adenergic α_2 sites (Table 1). Clearly none of the above drugs is an ideal tool for the study of 5-HT_{1C} receptor function.

Even fewer agonists have been used, but one, mCPP, is discussed in some detail later. One problem with the interpretation of human data derived from the use of these drugs is that their affinities for human receptors may differ from their rat equivalents. One example of this is the fifty-fold higher affinity that mesulergine has for rat as opposed to human 5-HT_2 receptors [21]. This may give mesulergine a fifty-fold greater affinity for the 5-HT_{1C} over the 5-HT_2 receptor in humans. In the same study ritanserin had a seven-fold lower affinity for rat than for human 5-HT_2 sites.

Table 1: Affinity values of 5-HT_{1C} receptor antagonists for 5-HT, adrenergic α_1 and α_2, dopaminergic D_2 and histamine H_1 receptors in mammalian brain membranes.

Drug	5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_{1D}	5-HT_2	5-HT_3	α_1	α_2	D_2	H_1
1-NP	7.2	6.6	8.3	7.8[b]	7.2	6.9	-	-	-	-
LY 53857	6.4	5.5	8.1	-	7.3	7.5[f]	-	-	-	-
Mesulergine	6.2	4.9	8.8	5.2	8.4	-	5.3[b]	6.1[b]	6.8[b]	5.2[b]
ICI 169,369	5.3	-	8.0[c]	6.3	7.8[d]	6.0[c]	6.2[d]	5.9[d]	6.9[d]	6.0[d]
ICI 170,809	< 6.0[g]	-	8.3[f]	-	9.1[g]	-	7.0[g]	-	6.1[g]	6.3[g]
Metergoline	8.1	7.4	9.2	8.3	9.0	-	7.0[a]	6.0[a]	7.2[a]	5.7[a]
Ritanserin	5.2	< 4.0	8.9	5.8	8.8	5.6[g]	7.9[g]	7.1[g]	7.5[g]	8.4[g]
Methysergide	7.6	5.8	8.6	8.4	8.6	4.5	5.2[a]	5.2[a]	6.3[a]	<6.0[a]
Mianserin	6.0	5.2	8.0	6.4	8.1	7.2	6.6[a]	6.8[a]	5.8[a]	8.3[a]
SR 46349B	4.9[i]	4.8i	6.9[i]	< 6.0[i]	8.2[i]	-	5.5[i]	6.0[i]	< 6.0[i]	5.3[i]
RP 62203	7.1[g]	< 6.0[g]	8.5[f]	-	9.9[g]	5.2[g]	8.4[g]	< 6.0[g]	6.4[g]	7.3[g]
Setoperone	5.6	5.3	7.3	-	8.6	-	-	-	-	-
Pirenperone	5.9	5.3	7.3	-	8.8	-	-	-	-	-
Altanserin	5.6	6.0	6.9	-	8.6	-	-	-	-	-
Cisapride	5.7	5.2	6.3	5.3	8.1	-	-	-	-	-
Ketanserin	5.9	5.7	7.0	6.0	8.9	3.6	7.5[a]	< 6.0[a]	6.3[a]	7.7[a]
Spiperone	7.2	5.3	5.9	5.3	8.8	3.6	-	-	-	-

Data taken from [16] or [423] except:

[a] Ref [15] [b] Ref [62] [c] Ref [100]
[d] Ref [250] [e] Ref [103] [f] Wood MD, personal communication
[g] Ref [17] [h] Ref [13] [i] pIC_{50} values from [18]

The 5-HT_{1C} receptor secondary messenger system

Palacios *et al.* [22] reported that activation of 5-HT_{1C} in the pig choroid plexus had no effect on adenylate cyclase activity. However 5-HT was found to cause the stimulation of phospholipase C and the breakdown of phospholipids in homogenates of this tissue [23], actions usually associated with the release of Ca^{2+} ions from the intracellular stores [24,25]. This effect was potently inhibited by the non-selective 5-HT_{1C}/5-HT_2 receptor antagonist mianserin but only by high concentrations of the selective 5HT_2 receptor antagonist [16] ketanserin and spiperone [23], suggesting 5-HT_{1C} receptor mediation. Subsequently Hoyer *et al.* [26] correlated the potency of twelve agonists and fourteen antagonists in inducing or inhibiting 5-HT-induced phosphoinositide (PI) hydrolysis in choroid plexus cells, with their

affinities for the 5-HT_{1C} receptor. Since 5-HT_2 receptors are also coupled to a PI hydrolysis secondary messenger system this is another common feature of the two receptors.

5-HT_{1C} receptor stimulation may also result in activation of Cl^- channels. Application of 5-HT to Xenopus oocytes injected with rat brain or choroid plexus messenger ribonucleic acid (mRNA) causes PI hydrolysis and increased intracellular Ca^{2+} levels. This in turn was shown to cause the opening of Ca^{2+}-dependent Cl^- channels [27-30]. The pharmacology of Cl^- ion channel activation by 5-HT in this system is most consistent with 5-HT_{1C} receptor mediation [28,29]. However there are several discrepancies such as the relatively high affinity of ketanserin and low affinity of cyproheptadine (Merck Sharp & Dohme) and mesulergine compared to that determined by receptor binding [16,28]. In Xenopus oocytes expressing mRNA from rat brain the effect of 5-HT on Cl^- currents was mimicked by the intracellular application of guanosine triphosphate α (GTP)-γ-S. Both effects were blocked by injection of the Ca^{2+} chelator ethylene glycol-bis(β-aminoethyl ether) N,N,N,N-tetraacetic acid (EGTA). The effect of 5-HT was also blocked by pertussis toxin which was shown to promote the adenosine diphosphate (ADP)-ribosylation of a GI-protein [31]. This data suggests that a Ca^{2+} dependent Cl^- ion channel is activated via a G-protein stimulation of phosphoinositide hydrolysis. 5-HT mediated stimulation of ion channels has also been observed in oocytes expressing mRNA from both human brain [27] and rat small intestine [32], although no pharmacological analysis was made. It remains to be seen whether 5-HT_{1C} receptors in the brain are coupled to Cl^- channels, or whether this coupling is artificially created by the expression of mRNA in an alien cell and its endogenous inositol phospholipid signalling system.

Evidence from Xenopus oocytes injected with both rat brain 5-HT_{1C} receptor and K^+ channel mRNA, suggests that 5-HT_{1C} receptors may modulate the function of K^+ channels. Thus in the presence of EGTA to suppress Cl^- ion channel activation, 5-HT causes an inward current, not found in oocytes injected with either mRNA alone [33], which is due to the closing of a class of K^+ channels [34,35].

5-HT_{1C} receptor molecular biology

The 5-HT_{1C} receptor was first cloned by Lubbert *et al.* [29] from rat choroid plexus tissue. The method used involved isolating rat choroid plexus mRNAs, fractionating them by gel electrophoresis and expressing them in Xenopus oocytes where stimulation of the 5-HT_{1C} receptor, formed from the desired mRNA, results in Cl^- ion channel opening. The mRNA thus identified had a molecular weight of 5000 daltons. Later Julius *et al.* [36] published the amino acid sequence of this receptor which contained 460 residues. The sequence revealed seven regions of hydrophobicity each of 20-30 amino acids. These regions would be expected to associate with the hydrophobic lipid membrane to form helical transmembrane domains. This arrangement is common to all members of the G protein-coupled receptor family of membrane proteins which include the 5-HT_2, 5-HT_{1A}, adrenergic β receptor and muscarinic acetylcholine receptors amongst others. The family is so called because the response to receptor activation is indirectly mediated by a class of GTP-hydrolysing enzymes allosterically coupled to the receptor. Thus receptor stimulation activates a G protein which in turn acts upon the cellular system [37]. A more recent study has suggested that the 5-HT_{1C} receptor in rat and mouse have an eighth transmembrane domain not found in other members of the G protein-coupled family [38]. Human 5-HT_{1C} receptor sequences have also been recently reported [39]. Both mouse and human sequences are very similar to the rat, the mouse amino acid sequence having 97% [38] and human 90% [39] homology. These small differences have not yet been observed to have great pharmacological significance.

One observation from the sequencing of the 5-HT_{1C} receptor was its resemblance to the 5-HT_2 receptor. In rat the overall homology is 51% as opposed to 35% for the 5-HT_{1A} receptor. When the seven transmembrane domains are compared this rises to 79% homology for the 5-HT_2 receptor [40]. In humans total 5-HT_2 and 5-HT_{1C} gene sequence homology was 50% and in transmembrane domains 80% [39].

It is of some interest that the 5-HT_{1C} receptor gene is located on the X chromosome, unlike 5 HT_2 or 5-HT_{1A} receptors [38]. This suggests that it may be involved in the effects of 5-HT on sexual differentiation [41].

5-HT_{1C} receptor distribution

Autoradiographic studies using [^{3}H]mesulergine in rat brain have demonstrated very high densities of 5-HT_{1C} receptor binding sites in the choroid plexus with roughly ten-fold lower densities in the hippocampus CA1 region, substantia nigra, globus pallidus, layer III of the cerebral cortex, olfactory cortex, lateral amygdaloid nucleus and thalamus [42]. This distribution is paralleled in mice [43]. A more detailed study of the human brain has also revealed a similar distribution. Here low levels were widely distributed in the following rank order of density: hypothalamus ventromedial nucleus > globus pallidus > hippocampus CA1 and CA3 > substantia nigra, nucleus accumbens, putamen > amygdala > thalamus. Other regions contained even lower densities [20,44].

One problem with the mapping of 5-HT_{1C} receptors is the high level of non-specific binding encountered with [^{3}H]mesulergine [44]. The mapping of 5-HT_{1C} mRNA is more specific and has allowed improved accuracy. Several studies have been conducted. In general these have confirmed receptor binding distributions. However some discrepancies have emerged, particularly the relatively high densities of mRNA in the septum, lateral habenula and subthalamic nucleus which are not matched by high levels of binding [43,45]. These may suggest differences in regional receptor turnover rates or reflect transport of mRNA from the cell body site of synthesis to the site of expression. Some discrepancies may be due to experimental differences. Thus Hoffman & Mezey [45] report high 5-HT_{1C} mRNa levels in rat dentate gyrus not seen by Molineaux *et al.* [46] or Mengod *et al.* [43], while Molineaux *et al.* [46] report high levels in the hippocampal CA1 region which were not seen by Hoffman & Mezey [45] or Mengod *et al.* [43].

The existence of 5-HT_{1C} receptors outside the brain has yet to be demonstrated. Only one model has been proposed: mediation of 5-HT-induced contractions of the rat stomach fundus [47]. This rests on the antagonist potency in this model of the older 5-HT_{1C}/5-HT_2 receptor antagonists such as mianserin, methysergide and pizotifen (Sandoz) but not specific 5-HT_2 receptor antagonists [48,49]. However there are a number of differences. Yohimbine and rauwolcine, which are also potent antagonists of 5-HT in the fundus [48], have little affinity for the 5-HT_{1C} receptor [16]. Also many 5-HT_{1C}/5-HT_2 receptor antagonists act as non-surmountable antagonists [48] making predictions of affinity difficult. Furthermore 5-HT stimulation of the fundus appears not to cause PI hydrolysis [50]. No 5-HT_{1C} mRNA was detected in the tissue [51] while extracted mRNA expressed in Xenopus oocytes inhibited cyclic adenosine monophosphate (CAMP) formation [52]. Recently Foquet *et al.* [53] reported that the rat stomach fundus gene is closely related to, but structurally distinct from, the 5-HT_2 and 5-HT_{1C} receptor genes. This receptor was not observed in brain tissue in further studies by this group [54].

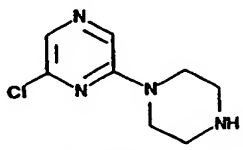
The expression of 5-HT_{1C}-like receptors from rat small intestine mRNA injected into oocytes [32] suggests that peripheral 5-HT_{1C} receptors may exist. 5-HT_{1C} receptor mediation of penile erections in rats, however, is likely to be centrally mediated [55].

MCPP - a putative 5-HT_{1C} agonist

MCPP is a metabolite of the widely prescribed antidepressant trazodone (Bristol-Myers Squibb) [56]. For this reason it has been considered ethical to administer the drug to humans. MCPP has principally been considered a 5-HT_{1B} agonist since it reduces 5-HT release in brain slices [57] and was observed to displace supposed 5-HT_{1B} receptor binding [58], although the preparation used would have contained 5-HT_{1C} receptors as well. In 1988 two prominent behavioural effects of mCPP, hypolocomotion [59] and hypophagia [60], were reported to be caused by 5-HT_{1C} receptor stimulation. This was consistent with receptor binding studies in which the drug had at least ten-fold selectivity over other 5-HT receptor subtypes including 5 HT_{1B} sites (Table 2). It was also consistent with the ability of mCPP to stimulate PI hydrolysis in the rat choroid plexus [61]. In this paradigm mCPP is reported to act with 65 to 90% of the efficacy of 5-HT whether rat [61] or pig [62,63] tissue is used, although both preparations have little receptor reserve [63,64]. MCPP's selectivity as a 5-HT_{1C} agonist is enhanced by its actions as a silent antagonist at cortical 5-HT_2 receptors mediating PI hydrolysis [61], in the 5-HT_2-mediated head twitch model in rats [65, 66] and in the 5-HT_2-mediated rat jugular vein model [67]. It is also an antagonist of rat vagus nerve [10] and rat cardiac [68] 5-HT_3 receptors. Against bovine 5-HT_{1D} receptors, Schoeffter & Hoyer [62] reported that it was a weak (30%) partial agonist with an estimated pK_B of 5.1. This was somewhat less than its binding affinity for the site; pK_I = 5.8–5.9 (Table 1). Recently two 5 HT_{1D} receptor subtypes have been identified 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ [69]. The affinity of mCPP for cloned human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors is reported to be 6.6 and 6.4 respectively [69]. The slightly higher affinity of mCPP for these cloned human 5-HT_{1D} receptors may reflect species differences or conceivably an artifact. MCPP has little affinity for 5-HT_{1E} or 5-HT_4 receptors.

The ten-fold selectivity of mCPP for 5-HT_{1C} over 5-HT_{1B} receptors evidenced by binding studies was not observed in a comparision of its efficacy in stimulating their respective secondary messengers [62] (Table 2) although selectivity over 5-HT_{1A}, 5-HT_{1D} and 5-HT_2 receptors was largely maintained. This was due to a large proportion of agonists tested having pEC_{50} values in the 5-HT_{1C} PI hydrolysis test roughly ten-fold lower than their binding affinities [26,62]. Since the degree of amplification needed to evoke a physiological or behavioural response in the different systems is unknown the relevance of this finding it unclear. Furthermore its relevance to mCPP's effects in man is also unclear. While 5-HT_{1B} receptors are not widely distributed in human tissue [44], a species homologue, the 5-$HT_{1D\beta}$ receptor, is found [69]. At the present time no data as to the effects of mCPP on this receptor's secondary messenger systems has been reported.

MCPP has also been reported to have some affinity for the adrenergic α_2 receptor (pK_D = 6.2) [70]. This is approximately forty-fold less potent than its affinity for 5-HT_{1C} receptors [62], although whether mCPP acts as an agonist or antagonist at these sites is unknown. Another ambiguity is the reported release of 5-HT *in vitro* by mCPP [71]. The importance of this effect has yet to be clarified but implies that intact presynaptic serotonergic function would be necessary to sustain an effect of mCPP mediated in this way. MCPP has very weak affinity for the adrenergic α_1 and β receptors, and for the dopamine D_2, muscarinic and benzodiazepine receptors [72].



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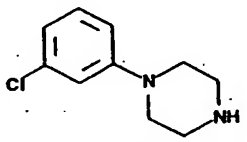


mCPP

Figure 2: 5-HT$_{1C}$ agonists

Table 2: Profile of the *in vitro* actions of mCPP

Receptor	Affinity of mCPP		Functional model		
	Rat or Pig (pK_i or pK_D)	Human (pIC_{50})	Model	pEC_{50} (pK_B or pA_2)	Efficacy (%)
5-HT$_{1A}$	6.6[a]	6.4[b]	Adenylate cyclase	5.9	40[c]
5-HT$_{1B}$	6.5[a]		Adenylate cyclase	6.5	60[c]
5-HT$_{1C}$	7.8[a]		Phosphoinositide hydrolysis	6.9	65[c]
	7.4[d]			7.1	90[d]
5-HT$_{1D}$	5.8[a]	5.9[b]	Adenylate cyclase	5.1	30[c]
5-HT$_{1D\alpha}$	6.6[i]				
5-HT$_{1D\beta}$	6.4[i]				
5-HT$_{1E}$	5.0[i]				
5-HT$_2$	6.7[a]	6.6[b]	Phosphoinositide hydrolysis	6.1**	0[c]
5-HT$_3$	7.0[a]		Vagus nerve	6.6***	0[b]
5-HT$_4$	5.0[i]				
α_1 adrenoceptor		5.5[b]			
α_2 adrenoceptor	6.2[f]	6.2[b]			
β adrenoceptor		5.6[b]			
Dopamine D$_1$		5.1[b]			
Dopamine D$_2$		5.0[b]			
Benzodiazepine	< 4.0[b]				
5-HT reuptake	< 4.0[b]				
5-HT release	0.1-1mM*[g]				

* Minimum effective dose
** pK_I
*** pA_2

Data taken from:

[a] [16] [b] [72] [c] [62] [i] [AM Brown, personal communication]
[d] [63] [e] [61] [f] [70]
[g] [71] [h] [10] [i] [69]

In conclusion, mCPP is a 5-HT$_{1C}$ receptor agonist and may have some selectivity for the site. In humans this selectivity may be promoted by the apparent absence of the 5-HT$_{1B}$ receptor although this may be offset by the higher affinity of the drug for cloned human 5-HT$_{1D\alpha}$ and 5-

$HT_{1D\beta}$ receptors [44]. The effects of mCPP in man have greatly contributed to perceptions of the utility of 5-HT_{1C} receptor ligands.

Table 3: Behavioural effects of mCPP in rats: models f 5-HT_{1C} receptor function?

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Reference]
Hypolocomotion	Metergoline	1-5	5-HT_1, 5-HT_2	Blocks[b,c] [59,229,235,426,427]
	Methysergide	5-10	5-HT_1, 5-HT_2	Blocks[b,c] [427]
	Mianserin	2	5-HT_{1C}, 5-HT_2, α_2	Blocks[b,c] [59,427]
	Cyproheptadine	2	5-HT_{1C}, 5-HT_2, H_1	Blocks [59] / No effect[b] [427]
	Mesulergine	0.5-4	5-HT_{1C}, 5-HT_2	Blocks[b] [427]
	Ketanserin	0.2-1	5-HT_2	No effect[c] [59,426]
	Ritanserin	0.1-2	5-HT_2	No effect[b] [59,426,427]
	Spiperone	0.01-0.05	5-HT_2, D_2	No effect?[b] [427]
	Cyanopindolol	0.2-8	5-HT_{1A}, 5-HT_{1B}, β	No effect[b] [59,427]
	Pindolol	2	5-HT_{1A}, 5-HT_{1B}, β	No effect[c] [59]
	Propranolol	5-16	5-HT_{1A}, 5-HT_{1B}, β	No effect[c] [59] / Potentiates [235]
	ICS 205,930	1	5-HT_3	No effect [59,427]
	MDL 72,222	0.5	5-HT_3	No effect [426]
	Idazoxan	1	α_2	No effect [59,427]
	PCA	Chronic	5-HT lesion	Blocks [427]
	PCPA	Chronic	5-HT depletion	No effect [Unpublished observation]
Hypophagia	Metergoline	1-5	5-HT_1, 5-HT_2	Blocks[d] [60,428,429]
	Mianserin	2-5	5-HT_{1C}, 5-HT_2 α_2	Blocks[d] [60]
	Cyproheptadine	10	5-HT_{1C}, 5-HT_2 H_1	No effect [60]
	Mesulergine	0.2	5-HT_{1C}, 5-HT_2	Blocks[d] [60]
	Ketanserin	0.2	5-HT_2	No effect[e] [60]
	Ritanserin	0.6	5-HT_2[a]	No effect[e] [60]
	Cyanopindolol	8	5-HT_{1A}, 5-HT_{1B} β	Blocks[e] [60]
	Propanolol	16	5-HT_{1A}, 5-HT_{1B} β	Blocks [60]
	ICS 205,930	1	5-HT_3	No effect [60]
	Idazoxan	1	α_2	No effect [60]
	Median Raphe lesion		Lesion	No effect [428]

Table 3: (cont.)

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Ref rence]
Penile Erection	Metergoline	0.02-0.2	5-HT_1, 5-HT_2	Blocks [231]
	Mianserin	0.02-0.2	5-HT_{1C}, 5-HT_2 α_2	Blocks [231]
	Cyproheptadine	0.1-1.0	5-HT_{1C}, 5-HT_2 H_1	Blocks [231]
	Mesulergine	0.02-0.2	5-HT_{1C}, 5-HT_2	Blocks [231]
	Ketanserin	0.5-1.0	5-HT_2	No effect [231]
	Ritanserin	0.1-0.5	5-HT_2 [a]	Blocks [231]
	Spiperone	0.1-1.0	5-HT_2, D_2	No effect [231]
	GR 38032F	1-10	5-HT_3	No effect [231]
Hyperthermia	Metergoline	0.5	5-HT_1, 5-HT_2	Blocks [233]
	Ritanserin	0.6[a]	5-HT_2	No effect [233]
	Pindolol	4	5-HT_{1A}, 5-HT_{1B} β	No effect [233]
	Propanolol	6	5-HT_{1A}, 5-HT_{1B} β	No effect [233]
Purposeless Chewing	Mianserin	1	5-HT_{1C}, 5-HT_2	Blocks [431]
	Ketanserin	5	5-HT_2	No effect [431]
	Spiperone	0.5	5-HT_2, D_2	No effect [431]
	ICS 205,930	10	5-HT_3	No effect [431]
	(–)Propranolol	20	5-HT_{1A}, 5-HT_{1B} β [f]	Blocks [431]

[a] Since the *in vivo* ID_{50} value for ritanserin against mCPP-induced hypophagia was 4.6 mg/kg *sc* [66], doses below this may be 5-HT_2 selective.

[b/c] Similar results obtained against TFMPP-induced hypolocomotion. Results from [b] [427] and [c] [229].

[d] Similar results obtained against TFMPP-induced hypophagia in freely feeding rats [430].

[e] Ketanserin 2.5 mg/kg partially blocked, cyanopindolol had no effect and ritanserin 0.5 and 1 mg/kg *ip* had an inverse dose related effect on TFMPP-induced hypopgagia [430].

[f] As (-)propranolol does not have pronounced specificity for 5-HT_{1A} and 5-HT_{1B} over 5-HT_{1C} sites [16], this dose may have blocked them all.

Possible therapeutic targets of 5-HT_{1C} receptor ligands:

Anxiety

Anxiety is widely observed in nearly all forms of mental illness. It is present in its purest form in anxiety disorders but is a noted feature of depression, schizophrenia and personality disorders. Four major types of anxiety have been characterised; generalised anxiety disorder (GAD), panic disorder with or without agorophobia, obsessive compulsive disorder (OCD), and other phobias. Several problems are associated with existing therapy. One of the most serious is the development of dependence in patients on long term benzodiazepine treatment. This leads to the induction of a marked anxiety on withdrawal [73]. Other problems include sedation and the interaction of this class of drugs with alcohol and barbiturates. Furthermore benzodiazepines are ineffective in the treatment of OCD [74], which only responds to chronic treatment with some antidepressants [75] and is then only partly effective. Chronic

antidepressant treatment is also efficacious in panic disorder [76-78]. However the side effect profile of this class of drugs (which includes anticholinergic, sedative and postural hypotensive effects for tricyclic antidepressants and hypotension and insomnia for monoamine oxidase inhibitors (MAOI)) has prevented their widespread use in these indications. Even the selective 5-HT reuptake inhibitor (SSRI) fluoxetine (Lilly) is associated with insomnia, nausea and asthenia [79].

Generalised anxiety disorder

Administration of mCPP to human volunteers caused anxiety [80-84]. In some subjects panic attacks were experienced [84,85]. The anxiogenic response to mCPP is accompanied by an increase of the stress sensitive hormones adrenocorticotrophic hormone (ACTH), cortisol and prolactin [80,86,87]. However there is some uncertainity over whether the hormonal changes are secondary to anxiety or not. Two studies of prolactin release suggest that it does follow peak anxiety [81,86] while one does not [84], although significant anxiety was not seen in this study.

MCPP administration to rats also induces anxiogenic-like responses in both the social interaction (SI) [88,89] and the elevated X-maze [Kennett, unpublished observations] models of anxiety, and decreases punished responding in a pigeon conflict model [90]. However in both the rat Geller-Seifter [91] and acoustic startle [92] models of anxiety the actions of mCPP were obscured by sedative or motor effects.

The anxiogenic response to systemic mCPP in the SI test was replicated after intra-hippocampal, but not intra-amygdaloidal, infusion [89]. This region has long been associated with the control of anxiety and is known to contain 5-HT_{1C} receptors [42,43,45,46]. The effect of mCPP, at least in the elevated X-maze, is not secondary to the release of 5-HT as it is not opposed by pretreatment with the 5-HT synthesis inhibitor p-chlorophenylalanine [Kennett, unpublished observations].

The pharmacology of the anxiogenic responses to mCPP in the rat SI and elevated X-maze tests is consistent with 5-HT_{1C} mediation. Thus in the SI test it is blocked by the non specific 5-HT_2/5-HT_{1C} receptor antagonists mianserin, cyproheptadine and metergoline (Farmitalia) (Table 1) but not by the selective 5-HT_2 antagonist ketanserin (Table 1) or by the 5-HT_{1A} and 5-HT_{1B} receptor antagonists [16] cyanopindolol (Sandoz) and (-)propranolol (ICI) [88]. The action of mCPP in the X-maze was similarly opposed by the non-selective 5-HT_2/5-HT_{1C} receptor blockers mianserin, LY 53857 and 1-NP [16], but not by the selective 5-HT_2 antagonists ketanserin and altanserin [16] nor by the 5-HT_{1A} and 5-HT_{1B} receptor blockers pindolol (Sandoz) [16] and cyanopindolol [Kennett, unpublished observations]. The effects of mCPP in both models was opposed by the benzodiazepine anxiolytic chlordiazepoxide (Roche) [88,93] reinforcing the interpretation that mCPP is anxiogenic. The anxiogenic effects of mCPP in both models were also attenuated by the 5-HT_3 receptor antagonists [16,94] ICS 205,930 (Sandoz) [88] and BRL 46470A (SmithKline Beecham) [93] in the SI and X-maze tests respectively. This is likely to be caused by the anxiolytic profile of these drugs [93,95]. Indeed mCPP might have more pronounced anxiogenic activity if it had less affinity for the 5 HT_3 site at which it is an antagonist (Table 1).

The results from rat models are consistent with the available clinical data. Thus the anxiogenic responses to mCPP have been reported to be blocked by the non-selective 5-HT_1 and 5-HT_2 receptor antagonists metergoline [85,96] and methysergide [85] and by the 5-HT_2/5-HT_{1C} receptor antagonist ritanserin (Janssen) [83]. This last report is of considerable interest, as

ritanserin has little affinity for other 5-HT receptor subtypes [16] and mCPP itself is a 5-HT_2 antagonist (see section on mCPP as a putative 5-HT_{1C} agonist).

The effects of antagonists on neuroendocrine responses to mCPP are similar. Metergoline and ritanserin both attenuate mCPP-induced prolactin secretion [83,87,96,97]. They also blocked the increase in cortisol [83,87,97]. Metergoline blocks the ACTH response as well [87]. Methysergide, however, was reported to block prolactin but not cortisol responses to mCPP [97].

Mediation of the anxiogenic effects of mCPP by 5-HT_{1C} receptor activation suggests that their blockade would be anxiolytic provided that some tone is exerted through the receptors under normal and/or anxiety provoking conditions. This hypothesis is supported by evidence from animal studies. In two recent studies [98,99], five non-selective 5-HT_2/5-HT_{1C} receptor antagonists, mianserin, 1-NP, ICI 169,369 (ICI), LY 53857 and pizotifen, (Table 1, [16,100]), were found to have anxiolytic-like actions in both the SI and Geller Seifter conflict tests. Compounds that did not share this property include: the selective 5-HT_2 antagonists ketanserin and altanserin, (Table 1); 5-HT_{1A} and 5-HT_{1B} receptor antagonists pindolol and cyanopindolol [16]; adrenergic α_2 receptor antagonist idazoxan (Reckitt and Colman) [101] or adrenergic α_2 antagonist and 5-HT_{1D} partial agonist yohimbine [101,102]; and H_1 antagonist mepyramine (May and Baker). The possibility of 5-HT_3 mediation of the effects is also unlikely as ICI 169, 369 [103] and LY 53857 (Table 1) have low affinity for this site, and 5-HT_3 antagonists are inneffective in the Geller-Seifter test [104,105]. Since the two tests have different motivational and aversive components the conclusion that these non-selective 5-HT_{1C} receptor antagonists are anxiolytic is strengthened. Similar findings have not been universally reported. The 5-HT_2/5-HT_{1C} receptor antagonist ritanserin, for instance, was inactive in one SI test [106], although the conditions used were inappropriate for the detection of anxiolysis [98]. The compound was active in one rat conflict procedure [107] but not in three others [108,109], although the paradigms used in the latter study were insensitive to benzodiazepines also. However, in the pigeon conflict test, claimed to be more sensitive to serotonergic drugs, ritanserin has shown an anxiolytic profile [90,109]. Mianserin, too, had no effect on SI where relatively high doses were used [110] but was active in the Geller-Seifter test when lower doses, similar to those of Kennett [98] or Kennett *et al.* [99], were used [111]. Another 5-HT_2/5-HT_{1C} receptor antagonist cyproheptadine [16] was also effective in some [112,113] but not all [108] conflict tests, while ICI 169,369 had some activity in the pigeon conflict test [114]. The non-specific 5-HT_1 and 5-HT_2 antagonists methysergide and metergoline [16] were not active in the SI test, albeit under different conditions [115], but were active in conflict tests [116-120]. The selective 5-HT_2 receptor antagonist ketanserin has also shown an anxiolytic profile in the pigeon conflict model [90]. This may reflect species differences in the 5-HT_{1C} receptor, or in the metabolism and disposition of ketanserin.

Another rat model claimed to be relevant to anxiety is the response to electrical stimulation of the periaqueductal gray (PAG). In humans this elicits unpleasant and fearful sensations [121] and in animals causes vigorous flight or defense reactions [122]. In this model mCPP acts as an anti-aversive agent; 5-HT_2/5-HT_{1C} antagonists mianserin, cyproheptadine and ritanserin as pro-aversive agents; and selective 5-HT_2 antagonists ketanserin, pirenperone and spiperone as anti-aversive agents [123]. Since mCPP is clearly anxiogenic both clinically and in other animal models the relevance of this paradigm is uncertain, but it may apply to a particular type of anxiety. Recently Beckett *et al.* [124] have reported mCPP to be pro-aversive when the PAG was chemically stimulated by homocysteic acid. This effect was blocked by mianserin.

The difference between these results and those obtained using electrical stimulation of the PAG may be due to the stimulation of fibres of passage by the latter technique.

Taken as a whole these results suggest that 5-HT_{1C} antagonists are anxiolytic in at least some animal models. This is consistent with reports of the clinical anxiolytic properties of mianserin [125–128] and the effectiveness of ritanserin in generalised anxiety disorder [129–131]. Metergoline, however, is not anxiolytic [75] and may be anxiogenic clinically [132]. This may reflect its non-specificity for 5-HT_1 subtypes [16] and possibly the different distribution of receptors in man and rat. It is of considerable interest that selective 5-HT_{1C} receptor antagonists have been claimed to possess anxiolytic activity, being active in the SI and Geller-Seifter test, in a recent SmithKline Beecham patent [500].

Panic Disorder

The administration of mCPP to normal volunteers evoked anxiety resembling panic attacks in some subjects [84,85]. In panic disorder patients, mCPP was found to induce panic attacks in roughly half of those treated. These were reportedly indistinguishable from those normally experienced [81,85,133–135]. The increase in anxiety and panic reported by these patients was also greater than that of healthy volunteers [85,133,134] although this did not reach significance in the study by Charney *et al.* [81]. However this group may have achieved a supramaximal response.

Neuroendocrine responses to mCPP in panic disorder patients followed a similar pattern. Thus Kahn *et al.* found that plasma cortisol responses to mCPP were enhanced [133], as were ACTH and prolactin in female, but not male panic disorder patients [136]. However cortisol, prolactin and growth hormone responses were not different from healthy volunteers in the study of Charney *et al.* [81] as observed for the anxiety response.

The above evidence has been used to argue the existence of hypersensitive 5-HT receptors in panic disorder. Since the anxiogenic effects of mCPP are probably 5-HT_{1C} receptor mediated (see above) these may be the hypersensitive 5-HT receptors in panic disorder. However the enhanced responses to mCPP could instead be secondary to hypersensitive anxiety mechanisms distal to 5-HT_{1C} receptors themselves. This view is supported by the ability of caffeine [135,137,138], yohimbine [139] and lactate [140], anxiogenic agents with differing modes of action to mCPP, to also induce a greater degree of anxiety in panic disorder patients, although not all induce robust increases in cortisol or prolactin [135]. The hypothesis may be further supported by the lack of clinical efficacy of the 5-HT_{1C} and 5-HT_2 receptor antagonist ritanserin in panic disorder [141] although an earlier open trial of the drug did suggest some benefit [142]. Furthermore the efficacy of tricyclic antidepressants [76] and the specific 5-HT reuptake inhibitor fluoxetine [77,78] after chronic administration may be mediated by down regulation of 5-HT_{1C} receptors (see section on depression).

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is characterised by obsessions (recurrent, intrusive thoughts) and compulsions (repetitive behaviours) such as ritualistic washing or checking which the patient recognises as senseless. The patients experience significant anxiety but the most common complication of primary OCD is depression [75]. OCD is refractory to benzodiazepine anxiolytics, despite reduced anxiety levels [74]. However chronic treatment with the antidepressant chlorimipramine (Geigy) [143,144] was found to ameliorate symptoms to a greater degree than other tricyclic and MAOI antidepressants [145]. Since chlorimipramine is a relatively selective 5-HT reuptake inhibitor [146] this suggested that a defective 5-HT

system might be involved, as did the effectiveness of treatment with the 5-HT precursor tryptophan [147] and the correlation of clinical efficacy of chlorimipramine with reduced CSF 5-hydroxyindoleacetic acid levels, but not plasma levels, of the drug [148]. Subsequently, chronic treatment with specific 5-HT reuptake inhibitors such as fluoxetine, zimeldine (Astra), sertraline (Pfizer) and fluvoxamine (Duphar) were also found to be effective anti-obsessional treatments [149,150] while the 5-HT releaser fenfluramine (Servier) can augment the therapeutic action of chlorimipramine [151]. Unfortunately, none of the treatments are effective in more than 50% of the patients and this is only reached after approximately 6 weeks treatment [145,149]. MAOIs, which acutely enhance extraneuronal 5-HT, are also clinically effective in OCD [145] although not in all studies [143]. But noradrenergic reuptake inhibitors are not effective[145].

The administration of mCPP orally to OCD patients provoked anxiety and this response was greater than in healthy volunteers [152]. The drug also exacerbated obsessive compulsive symptoms [96,152–154] which in some cases had been absent for several months, although this did not occur in the study of Charney *et al.* [155] in which intravenous administration was used. None of the studies reported the induction of panic attacks in OCD patients. The effect of mCPP on OCD symptoms was antagonised by metergoline [75,96] which is a non-specific 5-HT_1/5-HT_2 receptor antagonist [16]. Since mCPP and metergoline act as agonist and antagonist respectively at 5-HT_{1C} receptors, these findings may suggest that the receptors are in some way hypersensitive in OCD patients. Chronic administration of specific 5-HT reuptake inhibitors such as fluoxetine or MAOIs might therefore act by down-regulating these receptors, as suggested by evidence outlined in the section on depression and by the ability of chronic administration of fluoxetine and chlorimipramine to desensitise the behavioural effects of mCPP in OCD patients [157,158]. However not all evidence supports this hypothesis. Obsessive compulsive symptomology was not induced by MK 212 [156], an agonist at 5-HT_{1C} receptors [61] with roughly fifty-fold selectivity over 5-HT_2 receptors [16]. This may reflect the drug's poor selectivity over 5-HT_{1A} receptors [16] or its even higher affinity for the 5-HT_3 receptor (Table 3, [159]). Its affinity for many other sites is unknown and could also influence its effects on OCD patients, although in rats the stimulus cue of MK 212 generalized to mCPP and was blocked by metergoline and methysergide but not by specific 5-HT_2 receptor antagonists [160]. Another difficulty for the 5-HT_{1C} hypothesis of OCD is the failure of acute fenfluramine, the 5-HT releaser, to induce OCD symptomology in OCD patients [154,161]. Although this type of drug might be expected to stimulate many 5-HT receptor subtypes simultaneously, which could account for this finding, it too produces a stimulus in rats which generalizes to mCPP [160] and induces anxiety in rats by 5-HT_{1C} receptor stimulation [162]. It also has reasonable affinity for the 5-HT_{1C} receptor itself [163].

Evidence from neuroendocrine responses to mCPP is also inconsistent with 5-HT_{1C} receptor hypersensitivity in OCD. Patients had reduced cortisol responses to mCPP [152,156] and reduced prolactin responses in some [154,155,158] but not in all [152,154] studies. Responses of both hormones to MK 212 were also blunted [156]. Furthermore, although chronic fluoxetine [157] and chlorimipramine [158] abolished the ability of mCPP to increase obsessive and compulsive symptoms and anxiety, cortisol and prolactin responses were potentiated in the fluoxetine study [156], although increased plasma levels of mCPP could have been responsible [153]. Neuroendocrine evidence, therefore, suggests that 5-HT_{1C} receptors may be subsensitive in OCD in direct contrast to the behavioural data.

These apparent contradictions may be explained if the involvement of 5-HT_{1C} receptors in OCD symptomology resides in specific brain regions or if the hormonal responses to mCPP are not 5-HT_{1C} receptor mediated. The latter possibility seems unlikely, as clinically mCPP-

induced cortisol and prolactin secretion are blocked by metergoline [87,97] and the relatively selective 5-HT_2/5-HT_{1C} receptor antagonist ritanserin [83], although methysergide only blocked the prolactin response [97]. A third possibility is that a functional supersensitivity, which is either proximal or distal to the 5-HT_{1C} receptors, underlies OCD and that the receptors themselves are down regulated by compensatory mechanisms.

Table 4: Pharmacology of trifluoromethylphenylpiperazine (TFMPP), MK 212, Quipazine, 2,5-dimethoxy-4-iodoamphetamine (DOI) and (–)2,5-demethoxy-4-iodoamphetamine (–)(DOM); agonists at 5-HT_{1C} receptors

Receptor		5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_{1D}	5-$HT_{1D\alpha}$	5-$HT_{1D\beta}$	5-HT_{1E}	5-HT_2	5-HT_3
Drug	**Parameter**									
TFMPP	pK_D	6.5	6.9	7.3	6.6	7.1[g]	6.9[g]	5.2[h]	6.6[a]	
	pEC_{50}	6.7	6.9	6.8	5.8				6.1[b]	
	Efficacy	67.1	74.3	59.2	54.2				Ant[b]	
MK212	pK_D	5.3[c]	5.0[c]	6.2[c]	> 5.0 [f]			> 50[k]	4.8[c]	7.5[i]
	pDC_{50}			6.1[b]					4.7[b]	
	Efficacy			90[b]					80[b]	
Quipazine	pK_D	5.5	6.5	6.7	5.9				6.2	8.5
	pEC_{50}	5.2	6.2	6.2	5.7				5.0	
	Efficacy	Ant	Ant	63	Ant				80	Ant
DOI	pK_D	4.7[j]		7.8[d]	5.6 [j]			5.5 [h]	7.5[j]	
	pEC_{50}			7.0[d]						
	Efficacy			58[d]						
(-)DOM	pK_D			6.8[e]						
	pEC_{50}			6.1[e]						
	Efficacy			85[e]						

Values for pEC_{50} and efficacy (E_{max} as a percentage of that for 5-HT) for agonist activity, pK_B for antagonist efficacy and pK_D from receptor binding studies are given. The functional assay for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor was inhibition of forskolin-stimulated adenylate cyclase activity. The assay for 5-HT_{1C} and 5-HT_2 receptor function was stimulation of basal inositol phosphate accumulation in choroid plexus and cortical tissue, respectively. All data taken from [62] except:

[a] [16] [b] [61] [c] [424]
[d] [26] [e] [64] [f] G Price; personal communication
[g] [69] [h] [425] [i] [159] (pIC_{50}) [j] [432] [k] [AM Brown, Personal communication]

The effect of mCPP on OCD symptoms, unlike its actions in panic disorder (see above), is not typical of other anxiogenic drugs. Thus yohimbine [164], lactate [165] and caffeine [166] cannot induce or exacerbate obsessive compulsive symptomatology, suggesting the existence of a specific dysfunction. Interestingly, these symptoms are not induced in healthy volunteers. While the evidence points to this dysfunction possibly involving 5-HT_{1C} receptors, there is less evidence that an antagonist of these receptors would be of therapeutic benefit. Metergoline, the only 5-HT_{1C} receptor antagonist studied to date, was found to modestly reduce obsessive compulsive symptoms in one study [75] but not in a second [96]. The lack of effect of metergoline could reflect the drug's lack of speficity for 5-HT_{1C} receptors [16] (Table 1); indeed, in some clinical studies it was itself anxiogenic [132] and in one study it reversed the therapeutic action of chlorimpiramine, increasing anxiety and OCD symptomatology [167]. One possible property of metergoline that would be more prevalent in humans than in rodents is its agonist activity at 5-HT_{1D} receptors [168], the effects of which are, as yet, unknown. If 5-HT_{1D} receptor stimulation can induce OCD symptomatology, as has been suggested by Zohar & Kindler [169], this might underlie the action of mCPP which has agonist properties at 5-HT_{1D} receptors and relatively high affinity for the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ cloned human

receptors (Table 2). It might also be consistent with the failure of MK 212 to precipitate OCD symptomatology [156] as this drug has low affinity for the 5-HT_{1D} receptor (Table 3), although its affinity for human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors is unknown. However the effects of metergoline on OCD symptomatology are inconsistent (as outlined above) and yohimbine, another 5-HT_{1D} partial agonist [168], had no effect [164].

Another possibility is that metergoline could be a 5-HT_{1C} agonist at the human receptor. Alternatively the effects of 5-HT reuptake inhibitors and MAOIs could be caused by effects on sites other than the 5-HT_{1C} receptor.

Drugs of abuse

Alcoholism

Alcoholism is estimated to have a lifetime occurrence of 11-16% of the American population [170], and 5-HT has long been thought to influence this condition. Low cerebral spinal fluid (CSF) levels of the principal metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), have been observed in alcoholics [171,172]. This would seem to be trait-dependent as they were also observed in abstinent alcoholics [171] or in those suffering from withdrawal symptoms after one week of abstinence [173]. Banki [174,175] reported a negative correlation between 5-HIAA levels and number of days of abstinence.

Animal studies have provided further evidence. Levels of 5-HT and 5-HIAA were found to be reduced in some brain regions of alcohol-preferring rats [176]. Acutely, alcohol increases 5-HT release [177] and metabolism [178,179] in the striatum and increases 5-HIAA levels in several other brain regions including the nucleus accumbens [176] while reduced 5-HT turnover has been observed after chronic treatment [180]. Low 5-HT function has therefore been proposed to promote alcohol consumption. Treatments which increase serotonergic function might thus be expected to reduce alcohol consumption, and this has indeed been reported. Administration of the 5-HT precursors tryptophan [181] or 5-hydroxytryptophan (5-HTP) [176], the 5-HT releasing agent fenfluramine [176] and the 5-HT reuptake inhibitors fluoxetine [182–184] and sertraline [185], all reduce alcohol consumption when given acutely to rats. Intra-nucleus accumbens 5-HT has a similar effect [186]. The 5-HT_{1A} agonist 8-OH-DPAT [176,187,188], 5-HT_2 and 5-HT_{1C} agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) (Table 3, [176]) and 5-HT_{1B} and 5-HT_{1C} agonist 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) (Table 3, [176]) also reduce consumption. Conversely, treatments that reduce 5-HT function, such as the 5-HT depletor para-chlorophenylalanine (PCPA) [189,190], enhance consumption. However the non-specific 5-HT_1 and 5-HT_2 receptor antagonists methysergide and metergoline [191,192] had no effect, while the 5-HT neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) had inconsistent effects [193,194].

Clinical trials are in agreement with results from animal models. In particular the 5-HT reuptake inhibitors fluoxetine, zimelidine, and citalopram (Lundbeck) all reduced the mean daily alcohol consumption of moderate alcoholics. The magnitude of this effect while consistently observed was only 9-17% [195–197]. Interestingly, the effect had a rapid onset, unlike the antidepressant actions of these drugs. This suggests mediation by increased synaptic cleft 5-HT levels. The 5-HT_{1A} receptor agonist buspirone (Bristol-Myers Squibb) has also been shown to have modest clinical efficacy [198–200]. This could be mediated either by stimulation of postsynaptic 5-HT_{1A} receptors, by desensitisation of cell body autoreceptors and hence enhanced 5-HT release [201], or acutely by stimulating these autoreceptors and hence decreasing 5-HT release.

In view of the above evidence that enhanced 5-HT suppresses ethanol intake, the effects of mCPP on alcoholics are surprising. The drug was reported to induce an alcohol-like 'high' feeling in alcohol abstaining alcoholics and, in a third of the subjects, induced a craving to drink alcohol [202]. One explanation for these results, proposed by Sellers *et al.* [203], is that mCPP can induce an ethanol-like stimulus. This is supported by the reported similarity between the ethanol cue in a rat drug discrimination paradigm and that of TFMPP [204], a 5-HT_{1C}/5-HT_{1B} agonist resembling mCPP both pharmacologically (Table 3) and behaviourally in rats [59,60,88,205]. The perception of an alcohol-like stimulus in the absence of the full pharmacological effect may therefore cause craving.

An alternative explanation is that alcoholism is related to obsessive compulsive disorder [206]. Like alcoholism, OCD can be characterised by low 5-HT function [144,147], is ameliorated by specific 5-HT reuptake inhibitors (albeit after chronic administration [149]) and can be precipitated by mCPP (see above). It has also been suggested that the craving response to mCPP is secondary to the induction of anxiety [203], since alcoholism often coexists with anxiety [207]. This seems the least likely explanation, as anxiety induction was not noted in the Benkelfat *et al.* [202] study. However, the clinical efficacy of buspirone might be secondary to anxiolysis [208].

The pharmacology of mCPP (Table 2) suggests that 5-HT_{1C} receptors may account for these actions. Recent reports that the 5-HT_{1C} and 5-HT_2 antagonist (Table 1) ritanserin can reduce alcohol preference in rats [209] are possibly consistent with this. The effect was accompanied by increased water intake. It was not mediated by alcohol aversion nor by altered alcohol metabolism, and was not associated with body weight changes [209]. It may therefore specifically affect addictive mechanisms. Although this study reported effects at low doses, which might not be expected to block 5-HT_{1C} receptors *in vivo* [66], only high 5-HT_{1C} receptor blocking doses [66] were effective in a second model [210]. Ritanserin was also found to markedly reduce the alcohol intake of a small group of chronic alcoholics [211]. These patients reported that they had little difficulty in containing their consumption even after two weeks withdrawal from the drug. Mediation of these effects by 5-HT_2 receptor blockade seems unlikely: firstly mCPP is a 5-HT_2 receptor antagonist (Table 2), and secondly the specific 5-HT_2 receptor antagonist ketanserin (0.4 mg/kg *po* one hour pretest) did not affect rat alcohol preference in a recent study [210]. The reported ability of DOI and TFMPP, agonists at 5-HT_{1C} receptors, to reduce alcohol consumption in rat models [176] may be due to their anorexic [205,212], sedative [59,213] or, in the case of DOI, hallucinogenic [214] actions. These effects were not reported in the clinical study of Benkelfat *et al.* [202]. The predominance of the craving response to mCPP in alcoholics may suggest hypersensitive 'craving' mechanisms.

In conclusion, the opposing effects of mCPP and ritanserin, both clinically and in animal models, must be considered evidence of possible 5-HT_{1C} involvement. Further evidence must await the development and testing of more selective compounds. Indeed the effects of mCPP and ritanserin, while seemingly behaviourally specific and opposite, may be unrelated, as may be the case if ritanserin were acting as an anxiolytic (see above). The opposite nature of the effects of treatment which enhance 5-HT function such as 5-HT reuptake mechanisms (see above) and the mCPP/ritanserin studies, suggest the existence of several serotonergic mechanisms modulating alcoholism. When 5-HT function is enhanced at several receptor subtypes simultaneously the net result is alcohol intake inhibition. Conceivably this also occurs when 5-HT_{1C} receptors are selectively blocked. Given the modest clinical efficacy of 5-HT reuptake inhibitors there is considerable scope for new forms of treatment.

Oth r drugs of abuse

In addition to its effects on alcohol abuse, ritanserin has been anecdotally noted to be of use in patients withdrawing from other drugs of abuse [214]. This has led to an examination of its actions in rat models of cocaine and opiate dependence. Ritanserin was found to reduce both cocaine and fentanyl (Janssen) preference of rats [216,217]. The magnitude of the effect on cocaine was less than that observed for alcohol but greater than that observed with fentanyl [217]. This probably reflects the degree of reinforcement engendered by the drugs. Ritanserin does not interact with the cues for cocaine or fentanyl [216,217] which argues against any direct effects of the drug. Since drugs of abuse are thought to induce reinforcing effects by activating the dopamine reward pathways of the nucleus accumbens [218], it is of interest that ritanserin does not affect intracranial self-stimulation [216,217] which is thought to act on the same system. Ritanserin may therefore have a specific action on a reinforcing pathway common to drugs of abuse and perhaps distal to dopaminergic mechanisms of the nucleus accumbens. Whether this is 5-HT$_{1C}$ or 5-HT$_2$ receptor mediated is not yet clear.

Depression

A large body of evidence suggests that the serotonergic system is defective in depression. Most neurochemical and neuroendocrine studies of depressive patients are consistent with the existence of a serotonergic deficit, while SSRIs and MAOIs are clinically effective antidepressants and both increase extraneuronal 5-HT acutely (for review, see [219]).

One argument in favour of 5-HT$_{1C}$ receptor involvement in depression is the clinical efficacy of three 5-HT$_2$/5-HT$_{1C}$ receptor antagonists: mianserin [125,126,128], cyproheptadine [220] and ritanserin [221-223]. However, none of these drugs has been reported to exert immediate therapeutic action [221,223]. This may argue against simple 5-HT$_{1C}$ receptor blockade as a mode of action. Alternatively it might reflect a property of the disease state.

Clinically, the effect of treatments expected to enhance 5-HT$_{1C}$ function is also unclear. Thus mCPP administration to healthy volunteers did not cause depressive symptoms in most studies [80,81,84,134,224-226], with one exception [86]. In addition it does not potentiate depression in depressive patients and neither cortisol nor prolactin responses in these patients differed from that of healthy volunteers [133,134,226]. Indeed when given subchronically it ameliorated depressive symptomatology in elderly depressives [227]. These findings argue against direct 5-HT$_{1C}$ involvement in depression. However antidepressants may exert their therapeutic efficacy after chronic administration through adaptive changes to the serotonergic system [228], and, in particular, to the 5-HT$_{1C}$ receptor, as suggested by studies in rats. These involve models of 5-HT$_{1C}$ receptor function and are summarised in Table 5. Chronic treatments with the MAOIs phenelzine (Parke-Davis) or nialamide (Pfizer) have been reported to desensitise mCPP-induced hypolocomotion [229], a putative 5-HT$_{1C}$ mediated behaviour (Table 3, [59]). The MAOI tranylcypromine (SmithKline Beecham) reduced mCPP-induced penile erections [230], another putative 5-HT$_{1C}$ mediated response (Table 3, [231]) after chronic treatment, while chronic clorgyline reduced mCPP-induced hypophagia [232] and hyperthermia [233]. Of these last two paradigms mCPP-induced hypophagia is relatively well characterised as 5-HT$_{1C}$ mediated (Table 3, [59,66]) while hyperthermia is likely to be 5-HT$_{1C}$ mediated (Table 3, [233]). The effects of selective 5-HT reuptake inhibitors have been less extensively studied. One such drug, chlorimipramine [181] reduced mCPP-induced hypothermia after chronic treatment [233] while both chronic sertraline and citalopram reduced mCPP induced hypolocomotion [234]. However, chronic ORG 6997 (Organon) did not affect the rat penile erection model [230]. Noradrenergic reuptake inhibitors do not appear to share these properties. Thus, although imipramine (Ciba-Geigy) [181] reduced hyperthermic

responses to mCPP [233], it potentiated mCPP-induced hypolocomotion [235] and prolactin release but did not affect corticosterone or growth hormone release [236]. Also another noradrenergic reuptake inhibitor, desipramine (Ciba-Geigy) [181], did not alter the hypolocomotor response [229]. The atypical antidepressant iprindole (Wyeth Research) was also without effect after chronic administration [229]. These findings might be caused by altered metabolism or disposition of mCPP, but they suggest that, in rats, treatments that enhance extraneuronal 5-HT levels desensitise 5-HT_{1C} receptor function. This in turn may cause, or contribute to, their antidepressant efficacy. The therapeutic effect of subchronic mCPP [227] could therefore also be explained by 5-HT_{1C} receptor desensitization. Indeed, chronic mCPP desensitises mCPP-induced hypolocomotion [237-239] and changes in cerebral glucose metabolism [238] without altering its pharmacokinetic profile [238,239]. Chronic imipramine treatment is reported to reduce the hyperthermic effects of mCPP in humans [157] and in rats [233].

Table 5: The effects of chronic antidepressant treatments on putative rat models of 5-HT_{1C} receptor functional activity.

Treatment		Paradigm (mCPP-induced)	Effect	Reference
Class	Drug			
MAOI	Phenelzine	Hypolocomotion	Decrease	229
	Nialamide	Hypolocomotion	Decrease	229
	Tranylcypromine	Penile erections	Decrease	230
	Chlorgyline	Hypophagia	Decrease	232
		Hyperthermia	Decrease	233
SSRI	Chlorimipramine	Hyperthermia	Decrease	233
	Sertraline	Hypolocomotion	Decrease	234
	Citalopram	Hypolocomotion	Decrease	234
	ORG 6997	Penile erections	-	230
SNRI	Imipramine	Hyperthermia	Decrease	233
	Desipramine	Hypolocomotion	Increase	235
		Hypolocomotion		229
Atypical	Iprindole	Hypolocomotion		229

MAOI: monoamine oxidase inhibitor
SNRI: selective noradrenergic reuptake inhibitor
SSRI: selective serotonin (5-HT) reuptake inhibitor
Atypical: atypical antidepressant

This may suggest that 5-HT_{1C} receptors can be desensitised by this drug or that body temperature is affected by some other mechanism. Whether all these results can be safely interpreted as evidence of 5-HT_{1C} receptor desensitization awaits studies of 5-HT_{1C} receptor binding and PI hydrolysis.

Finally, the specific 5-HT reuptake inhibitor fluoxetine (a racemic mixture) and its (-) isomer have been shown to have some affinity for the 5-HT_{1C} site [240]. Since this is roughly ten-fold less than their affinities for the 5-HT reuptake site it may not explain their antidepressant efficacy. Fluoxetine is metabolised to the long-acting metabolite norfluoxetine. This too has

been found to bind to 5-HT_{1C} receptors, and a patent for its use in feeding disorders, OCD, alcoholism, sleep disorders and migraine has been published [502].

In conclusion, the evidence for a role for 5-HT_{1C} receptors in depressive illness is at present neither wholly consistent nor complete. The therapeutic benefit of ritanserin (and presumably mianserin and cyproheptadine) may be secondary to improved sleep, anti-anxiety and energy restoring properties. Some of these at least may not be 5-HT_{1C} mediated.

Migraine

When mCPP was administered to bulimic patients, migraine-like headaches were reported eight to twelve hours later [241]. This response was correlated with plasma levels of mCPP and was more pronounced in patients with a personal or family history of migraine, an effect confirmed in a recent study of migraine patients [242]. Migraine patients given mCPP had enhanced cortisol and temperature responses [242]. Fozard & Gray [243] have argued that 5-HT_{1C} receptor stimulation might be an important step in the pathogenesis of migraine for two reasons: firstly, mCPP activates 5-HT_{1C} but antagonizes 5-HT_2 receptors (see mCPP section). and secondly, methysergide pizotifen, mianserin and cyproheptadine, all of which are non-specific 5-HT_{1C} and 5-HT_2 receptor antagonists are clinically effective antimigraine agents, but the selective 5-HT_2 antagonist [16] ketanserin is not [244]. Recently Brown *et al.* [63] have demonstrated that two effective antimigraine agents, ergotamine (Wellcome) and dihydroergotamine (Sandoz), are also potent 5-HT_{1C} agonists but only occasionally induce headaches [245]. However, this may be due to the additional potent 5-HT_1-like constrictor activity of these drugs on large dilated cerebral arteries [63], which may confer antimigraine efficacy [245], this action is shared by sumatriptan (Glaxo), a novel antimigraine agent [246]. Since both drugs also activate other receptors (e.g. α adrenoceptors and dopamine receptors) these could conceivably mediate their effects [247]. It could also be argued that the α_1 adrenoceptor blocking activity of ketanserin (Table 1) prevented antimigraine efficacy. The relationship of 5-HT_{1C} receptors to the clinical efficacy of the 5-HT_{1C}/5-HT_2 receptor antagonists may also be disputed since they too have additional actions. Thus cyproheptadine and pizotifen have similar and appreciable affinities for dopamine, muscarinic cholinergic and α_1 adrenoceptor sites, and lower affinities for α_2 adrenoceptors (Table 1). They also have an affinity for histamine H_1 receptors equal to that for 5-HT_2 and 5-HT_{1C} sites (Table 1, [15]). Mianserin, too, has affinity for histamine H_1 receptors and lower affinity for both α_1 and α_2 adrenoceptors, but has low affinity for dopamine receptors and is inactive at cholinergic receptors (Table 1, [15]). Methysergide, however, has little affinity for histamine, α adrenoceptors or cholinergic receptors (Table 1, [15]). These four drugs, therefore, only share high affinity at the 5-HT_2 and 5-HT_{1C} sites, and the lack of clinical efficacy of histamine H_1, cholinergic, dopaminergic or α adrenoceptor antagonists [248] suggests that 5-HT_{1C}/5-HT_2 receptors alone are clinically relevant. The modest antimigraine efficacy of ICI 169,369 [249], another relatively specific 5-HT_2 and 5-HT_{1C} receptor antagonist [100,250], may be attributable to the dose used, while the clinical efficacy of chronic administration of 5-HT reuptake inhibitors such as amitriptyline (Merck Sharp & Dohme) [251] and fluoxetine [252,253] as migraine prophylactics may be caused by down-regulation of 5-HT_{1C} receptors (see section on depression and Table 5).

One interesting observation of the migraine-precipitant action of mCPP is the long time interval between administration and headache; peak mCPP concentrations were seen two to three hours after administration [241,242], whereas headache occurred up to twelve hours later.

This suggests an indirect mode of action and may be consistent with the prophylactic but not acute efficacy of 5-HT_{1C}/5-HT_2 receptor antagonists in migraine [243].

In conclusion, 5-HT_{1C} receptors may be involved in migraine. Further proof awaits the development of more specific compounds and further testing of existing drugs.

Sleep Disorders

In man, the serotonergic system has been considered hypnogenic. Treatments that enhance 5-HT function, such as the administration of the 5-HT precursors tryptophan [254,255,256] or 5-hydroxytryptophan (5-HTP) [256,257], increase either sleep time, the duration of slow wave sleep (SWS) or the duration of rapid eye movement sleep (REMS). Conversely the 5-HT depleter PCPA reduces REMS [258]. In cats, PCPA or 5-HT neurotoxic lesions can lead to total insomnia that can be reversed by 5-HTP [256]. As with many other functions of 5-HT, the recognition of 5-HT receptor subtypes has suggested that 5-HT may have differing effects on sleep depending on which subtype is studied. 5-HT_{1A} receptor agonists, for instance, increase wakefulness in both rats [259,260] and humans [261].

MCPP reduced total sleep time, sleep efficiency, SWS and REMS in two clinical studies [262,263]. Wakefulness was increased and subjective behavioural effects of mCPP seemed more prominent than in patients given mCPP during waking hours [262]. This may reflect the absence of environmental distraction. The effects of mCPP are consistent with reports that the 5-HT reuptake inhibitors zimelidine and indalpine (Groupe Pharmuka) also reduce total sleep time and REMS when given acutely [264]. In rats the mixed 5-HT_2/5-HT_{1C} agonist 2,5-dimethoxy-4-methylamphetamine (DOM) (Table 3) reduced both SWS and REMS [265]. The effects of the 5-HT reuptake inhibitor zimeldine are more complex. Initially it is reported to increase wakefulness and reduce REMS but after roughly two hours it enhances SWS [266]. Other 5-HT reuptake inhibitors, such as fluoxetine [267], indalpine [268] and alaproclate (Astra) [269], also reduce REMS and can enhance SWS [267,270]. The biphasic effects of this class of compounds is likely to reflect the stimulation of different 5-HT receptor subtypes by the released 5-HT. The increased wakefulness is unlikely to be 5-HT_2 or 5-HT_{1C} receptor mediated as it is not blocked by ritanserin [266]. Curiously, TFMPP given to rats reduced REMS but also increased SWS in the second hour after administration, although this effect was not dose-dependent [267]. The drug's profile of action was thus dissimilar to that of mCPP in humans but similar to 5-HT reuptake inhibitor; its action may therefore be due to 5-HT releasing properties [71].

The effect of drugs with 5-HT_{1C} antagonist properties is clearer. The 5-HT_2 and 5-HT_{1C} receptor antagonist, ritanserin, increases SWS, reduces sleep onset latency and improves subjective sleep quality in both young [272-274] and old [275] healthy volunteers. REMS is reduced in some [272,276] but not all [275,277] reports. A shift from early stage SWS to later, deeper SWS stages is generally reported [272,273,275-277]. Ritanserin has also proved efficacious in insomniac patients [278] and patients suffering from dysthymia (depressive neurosis) [277]. The drug achieved these effects acutely [273,275,276,279], chronically [273,275,277] and dose-dependently [276]. Only Adam & Oswald [275] reported withdrawal wakefulness. Other drugs with 5-HT_{1C} antagonist actions such as mianserin [280], cyproheptadine [281,282] and pizotifen [283] have similar effects, but methysergide [284] and metergoline [282] do not. This may reflect the lack of specificity of these compounds (Table 1, [16]) such as their 5-HT_{1D} partial agonist actions [168]. In rats, too, ritanserin increases SWS [265,266,285] although not always significantly [18]. However, some studies suggest that the deepest phase of SWS (SWS2) is increased but total SWS is not [266,285] and not all report

significantly reduced wakefulness [18,266]. As in clinical studies, REMS was reduced [18,265,285] although not universely [266]. Only one study of the effects of two other 5-HT_2/5-HT_{1C} receptor antagonists with an otherwise relatively clean profile of action, ICI 169,369 [250] and ICI 170,809 (Table 1), has been published. However while they increased REMS latency, as did ritanserin, ICI 169,369 had no effect and ICI 170,809 had little effect on SWS, although in the same study ritanserin reduced it [286]. Unfortunately SWS in this study was not subdivided into SWS1 and SWS2. Thus both antagonists might have increased SWS2 as seen by others. The effect of ritanserin on all sleep stages can be reversed by the 5-HT_{1C}/5-HT_2 agonist DOM [287]. Recently the effect on rat sleep patterns of SR 46349B, a relatively selective 5-HT_2 receptor antagonist (Table 1) was studied. This drug also reduced REMS and increased REMS latency, as did ritanserin [18]. This suggests that 5-HT_2 receptor antagonism mediates this effect. As neither SR 46349B nor ritanserin clearly affected SWS or wakefulness in this study it is not possible to decide whether these functions are 5-HT_2 or 5-HT_{1C} receptor mediated [18].

The shift in sleep pattern derived from ritanserin and other 5-HT_2/5-HT_{1C} receptor antagonists is subjectively reported to be beneficial and refreshing despite the reduced amount of REM sleep. The effects are also not associated with sedation [272]. Given the largely opposite effects of mCPP it seems possible that 5-HT_{1C} receptors might mediate these actions. Should reduced REMS be caused by 5-HT_2 receptor blockade, as suggested by the results of Rinaldo-Carmona *et al.* [18], and should increased SWS and reduced wakefulness be 5-HT_{1C} receptor mediated, then selective 5-HT_{1C} antagonists could be of particular therapeutic use in the treatment of sleep disorders. Further trials with more selective drugs are awaited.

Feeding Disorders

Administration of mCPP and TFMPP to food-deprived [60,428,430] or freely feeding [205] rats reduces subsequent food, but in the case of mCPP, not water [288] intake. The effect is not secondary to anxiety as it is not reversed by benzodiazepine anxiolytics [88]. Nor is it likely to be secondary to hypolocomotion as, unlike hypophagia, the effect is not blocked by either cyanopindolol or (–)propranolol [60]. Also TFMPP administration into the hypothalamus causes hypophagia only [289]. Since the hypophagia was not blocked by the antiemetic trimethobenzamide, mCPP is unlikely to induce nausea [290]. The accelerated appearance of the postprandial satiety sequence following both mCPP and TFMPP suggests that a satiety mechanism is probably responsible for their hypophagic actions [Kitchener & Dourish, unpublished observations].

The action of mCPP was blocked by the non-selective 5-HT_2/5-HT_{1C} receptor blockers metergoline, mianserin, mesulergine and 1-NP but not by the selective 5-HT_2 antagonist ketanserin or 5-HT_3 antagonist ICS 205,930 (Table 4, [60]). Inhibition of mCPP-induced hypophagia by ten antagonists was found to correlate only with their affinities for the 5-HT_{1C} site [66]. Studies on the pharmacology of TFMPP-induced hypophagia have produced a less clear discrimination between the effects of 5-HT_{1C} and selective 5-HT_1 receptor antagonists (Table 3, [430]). MK 212 also reduces feeding in rats [291] but the mechanism of action is unknown. The hypophagic effects of DOI [292] and quipazine (Miles Scientific) [293], both of which have high affinity for the 5-HT_{1C} site [16,26], have been reported to be mediated by 5-HT_2 receptors because they are ketanserin sensitive.

This may reflect differences in experimental design but is most likely to be secondary to response competition between feeding and the behavioural effects of 5-HT_2 receptor

stimulation, one possibility being hallucination [214]. Indeed DOI, at least, disrupts the postprandial satiety sequence [294] while quipazine reduces water intake also [288].

The effects of 5-HT_1/5-HT_{1C} antagonists have also implicated 5-HT_{1C} receptors in the control of food intake. Mianserin, cyproheptadine and 1-NP all increased the food intake of freely feeding rats over four hours as did mesulergine, albeit not significantly [60]. Likewise Dourish *et al.* [295] observed increased food intake after administration of metergoline, methysergide, mianserin and methiothepin. Metergoline, ritanserin and methysergide increased the consumption of palatable wet mash in rats partially sated prior to drug injection [296]. In contrast, the specific 5-HT_2 antagonist ketanserin had no effect on food intake in freely feeding rats [59,295]; neither did ritanserin at low doses [295,297] which may not block 5-HT_{1C} receptors [66]. Increased food intake is only seen under conditions of satiety where low rates of feeding occur. Under conditions of high feeding rates none of these drugs was effective [60,296]. This is consistent with mediation by blockade of satiety signals and may explain the contradictory findings of cyproheptadine's hyperphagic actions [298,299]. It is also of interest that the hyperphagic effects of these compounds has only rarely been observed to increase daily food intake or body weight [60,295,300-302], the exceptions being metergoline [295] and high doses of ritanserin [297]. This may suggest the presence of compensatory mechanisms.

In healthy volunteers or bulimics, mCPP has not been reported to affect appetite [303] possibly due to the short nature of most studies which are not designed to elicit changes in appetite. Since mCPP-induced anxiety is seen at doses ten-fold less than those necessary for hypophagia in rats [60,205], the doses used clinically may have been too low. However fenfluramine, a drug that enhances synaptic cleft 5-HT, is a noted, clinically effective anorexic agent [304]. It has been claimed to act via 5-HT_2 receptors in rats as it was blocked by ketanserin [305], but this was not confirmed by Neil & Cooper [288]. This group concluded that fenfluramine anorexia was 5-HT_1, but not 5-HT_{1A} or 5-HT_{1B}, mediated. However they could not block the effects of fenfluramine with the non-specific 5-HT_2/5-HT_{1C} receptor antagonist ICI 169,369 (Table 1, [17,100,250]) and only achieved a modest non-significant antagonism with mianserin. Consistent with these results were those of Garattini *et al.* [306], which showed antagonism of fenfluramine by metergoline but not by doses of ritanserin that might be specific for 5-HT_2 receptors [66]. However, a firm attribution of fenfluramine's actions (or at least a component of them) to 5-HT_{1C} receptor stimulation is not possible at present, although the drug has considerable affinity for the 5-HT_{1C} receptor [163] and has been reported to cause anorexia in rats pretreated with the 5-HT synthesis inhibitor p-chlorophenylalanine [307]. This suggests that the drug may act directly on postsynaptic 5-HT_{1C} receptors.

A second class of drugs that increase synaptic cleft 5-HT, the specific 5-HT reuptake inhibitors, are also clinically effective anorexic agents [308,309]. Fluoxetine [310-312], paroxetine (SmithKline Beecham) [309], zimelidine (Astra) [313], RU 25591 (Roussel UCLAF) [314] and sertraline [315,316] are hypophagic in rodents. Like fenfluramine the mode of action of these drugs is uncertain. Although the effect of sertraline was blocked by metergoline and methysergide, but not ketanserin [315], fluoxetine was not blocked by metergoline or LY 53857 [317], both of which are non-specific antagonists of 5-HT_{1C} receptors (Table 1). The effect of drugs which enhance extraneuronal 5-HT may be mediated via more than one 5-HT receptor subtype. Thus 5-HT can reduce food intake when injected into the paraventricular nucleus of the hypothalamus [318] or when given peripherally [319]. Both 5-HT_{1B} and 5-HT_{1C} receptors may mediate central hypophagic mechanisms [60,289], while 5-HT_2 receptors may mediate them peripherally [297,319,320]. The above evidence shows that the hypophagic actions of treatments which may enhance 5-HT_{1C} receptor function

are not well characterised in species other than rodents. Clinically effective anorectic agents may therefore attain their efficacy via mechanisms other than 5-HT_{1C} receptor stimulation.

Obesity

The hypophagic effects of 5-HT_{1C} receptor stimulation might be applied as an aid to weight loss, particularly where obesity is life threatening, as in those with cardiovascular disease. The 5-HT reuptake inhibitor fluoxetine has been shown to induce weight loss in obese patients [321-323] albeit not of great magnitude. Fenfluramine has long been recognised as an effective anorexic agent [304]. This drug achieves its anorexic response rapidly to give a new body weight set point which is often lost on withdrawal. Since the drug can induce 5-HT lesions [304], albeit at high doses, alternative therapies might well be more acceptable.

Bulimia Nervosa

Another possible indication is Bulimia Nervosa. This disorder is estimated to affect 1.3-10.1% of American women [79] and is characterised by compulsive eating binges followed by self-induced vomiting, laxative abuse, or other methods to prevent weight gain. It can cause serious morbidity and even mortality. Fenfluramine has been claimed to have beneficial effects in bulimics, reducing bingeing [324] in one acute study. A second study observed reduced bingeing within a week of chronic fenfluramine administration [325]. In both studies fenfluramine may have acted by a direct reduction of feeding behaviour, as Blouin *et al.* [325] reported a reduction in caloric intake in the fenfluramine treated patients. Antidepressants represent a second class of treatment. Thus monoamine oxidase inhibitors such as phenelzine [326] and isocarboxazid (Roche) [327], which would be expected to increase extraneuronal 5-HT levels, are clinically effective. The specific 5-HT reuptake inhibitor fluoxetine is also effective [79,328]. Interestingly so is trazodone [329], which could act via its metabolism to mCPP [56]. The onset of fluoxetine's therapeutic effects is rapid [79] suggesting that, as with fenfluramine, appetite suppression may be involved. This is consistent with the reported relapse of two fluoxetine treated patients when given the 5-HT_{1C}/5-HT_2 receptor antagonist cyproheptadine [330]. However the noradrenergic reuptake inhibitors [146] imipramine [331], desipramine [332] and nomifensine (Hoechst) [333] are also effective, which could reflect the considerable overlap between depression and bulimia [328]. One antidepressant that was not effective in the treatment of bulimia was mianserin [334]. Since blockade of 5-HT_{1C} receptors by this drug [16] may enhance appetite (see above and the following section) this may not be surprising. However, chronic administration of antidepressants that enhance extraneuronal 5-HT may down-regulate 5-HT_{1C} receptors (see section on depression and Table 5), which could detract from efficacy. The possibility remains that 5-HT_{1C} receptor agonists might be of use in the treatment of Bulimia Nervosa.

Anorexia Nervosa

Clinically the non-specific 5-HT_{1C}/5-HT_2 antagonists cyproheptadine [301,302,335,336] and pizotifen [337,338] stimulate appetite. Both of these drugs also share a high affinity for histamine receptors (Table 1, [15]). However mianserin, methysergide and metergoline are not reported to increase weight [306,339]. These discrepancies might result from the non-specific nature of the drugs. The effect of the relatively specific 5-HT_{1C}/5-HT_2 receptor antagonist ritanserin might therefore be more relevant. Out of six large clinical trials with this drug, only one reported mild weight gain as a side effect [223] and this was tolerated after the first month. Another study [131] observed one case of increased appetite in twenty-two patients given 5 mg/kg daily for four weeks but other groups using higher [130,141,221] or similar doses [129] did not. No effects on appetite were reported in several smaller trials [272,275,279].

Furthermore, no alterations in appetite were observed in a study with ICI 169,369 on migraine [249]. One reason for the discrepancy between the effects of cyproheptadine and pizotifen and the studies of ritanserin may be that the latter were not set up to study appetite, which might thus have been overlooked. Alternatively the expected increase in appetite may be mild in most patients.

The above properties suggest that 5-HT_{1C} receptor antagonists might be of use in the treatment of anorexia nervosa. However, to date, no drug has consistently proved effective in this disorder. If appetite stimulation could improve the symptomology of anorexia one would predict that 5-HT_{1C} receptor antagonists or chronic treatment with antidepressants which enhance extraneural 5-HT might prove effective. Since neither the 5-HT_{1C}/5-HT_2 receptor antagonist cyproheptadine [340,341,342] nor the 5-HT reuptake blocker chlorimipramine [343] had therapeutic value in anorexics, this seems unlikely.

5-HT_{1C} receptors and feeding disorders: Summary

In conclusion 5-HT_{1C} receptor stimulation is very likely to mediate hypophagia. This might suggest therapeutic utility in obesity and in the control of binge eating in bulimics. Unfortunately the anxiogenic properties of 5-HT_{1C} receptor agonists might prove a significant contraindication in the absence of any evidence that 5-HT_{1C} receptor subtypes exist that differentiate between the two actions. The possibility of tolerance to repeated administration of 5-HT_{1C} receptor agonists, as reported by Sills *et al.* [237], Freo *et al.* [238] and Ulrichsen *et al.* [239], might also be a problem. 5-HT_{1C} receptor blockade may produce increased appetite and weight gain. Drugs with these properties could therefore prove useful in the treatment of anorexia nervosa.

Cognition impairment

Although data on the role of 5-HT in learning and memory has been inconsistent, it is generally thought treatments that enhance 5-HT function led to impaired learning and memory [344]. It was therefore surprising when animal studies with 5-HT reuptake inhibitors such as alaproclate, zimeldine [345] and fluoxetine [346,347] observed cognitive enhancement after acute administration. Altman *et al.* [348], however, reported that the effects of alaproclate and zimeldine were opposed by pretreatment with quipazine, a 5-HT agonist, but not affected by cyproheptadine. They speculated that the effects of 5-HT reuptake inhibitors may be mediated by effects other than enhanced extraneuronal 5-HT [348].

Clinically, a number of studies have reported cognition-enhancing effects of reuptake inhibitors. Thus chronic citalopram (Lundbeck) improved concentration and absent-mindedness in demented patients [349] but this effect was not reproduced in a second larger study [350]. Chronic fluoxetine enhanced memory function in depressive patients in two studies [351,352] but not in a third [353]. However, as depression impairs cognition [351], these effects may be secondary to clinical improvement. Chronic zimeldine attenuated alcohol-induced memory impairment [354] and chronic fluvoxamine was reported to improve memory task performance in patients with alcohol amnesic disorder [355]. In healthy volunteers neither acute [356,357] nor subchronic fluvoxamine had any effect on learning and memory performance [358]. Chronic clomipramine enhanced verbal fluency, the ability to recognise nonsense words and motor function [359], while acute sertraline was considered to induce an 'alerting' response [360]. However in elderly volunteers subchronic fluvoxamine had little effect on psychomotor function [361] as did subchronic treatment with sertraline which, in addition, had no effect in memory tests [362]. The studies seem to suggest that clinically, chronic treatment with this class of drugs is more likely to produce enhanced cognition. This

may therefore be caused by the induction of neurochemical changes such as receptor down-regulation (see section on depression).

MCPP has been administered to Alzheimer's disease patients and produced an elevated anxiety response compared with normal age-matched volunteers at a higher [225] but not at a lower [224] dose. Cognition was also impaired to a greater extent at the higher dose [225] but only the lower dose of mCPP was found to worsen episodic memory of the elderly volunteers [224]. These effects could well be secondary to anxiety or light-headedness/dizziness [84,224,225]. MCPP-induced cortisol and prolactin release was not altered in Alzheimer patients after either low [224] or higher [225] doses.

Drugs with 5-HT_{1C} receptor antagonist properties have been reported to enhance cognitive performance in some animal studies. Thus post-training mianserin, metergoline and methysergide improved memory of mice for an aversive behaviour [363]. Mianserin also attenuated age-induced deficits in passive avoidance retention of rats [264] and protected rats against an hypoxia-induced deficit [347]. These effects are probably 5-HT_2 mediated, as the selective 5-HT_2 receptor antagonist ketanserin [16] had similar effects in all three models [363,364,367].

Clinically, chronic mianserin tended to impair the performance of both psychomotor and memory tests [358,361,362]. This effect was thought to be secondary to the drug's sedative properties and was less pronounced after several days of treatment. Sedative properties are common to most of the older 5-HT_{1C}/5-HT_2 receptor antagonists due to their affinity for histamine H_1 receptors (Table 1) and was thought to account for the psychomotor retarding effects of acute cyproheptadine, although memory was unaffected in this study [365]. One other such drug, ritanserin, has been reported to enhance motivation and increase subjective energy levels [221]. At present, therefore, there is little evidence to support a role for 5-HT_{1C} receptors in cognition.

Schizophrenia

MCPP has been reported to increase [366-368], have no effect [369], or decrease [370] psychotic symptomology. Blunted ACTH and prolactin responses to mCPP have been reported by Iqbal *et al.* [368] but were not seen in other studies [366,369,370], although Kahn *et al.* [370] reported blunted temperature responses to mCPP. Negative symptoms were unaltered by mCPP [366].

Conversely ritanserin has been reported to reduce negative/affective symptoms in schizophrenia (anergia, anxiety/depression, activity, hostility [221,371,372]), as has cyproheptadine [373]. Ritanserin is also reported to reduce neuroleptic-induced extrapyramidal side effects [374] and those induced by the dopamine precursor DOPA in patients with Parkinson's disease [375,376]. Furthermore it may prevent neuroleptic-induced akathesia [377]. These properties are shared by the atypical antipsychotic clozapine, on which basis it is considered to be superior to classical neuroleptic agents [378]. Since, like ritanserin, clozapine has high affinity for 5-HT_2 receptors (Table 6, [378]) and an even higher affinity for 5-HT_{1C} sites (Table 6, [379]), these might mediate their actions. Indeed a high affinity for the 5-HT_{1C} receptor is also possessed by several other putative atypical [380] antipsychotic agents including tiospirone (Mead Johnston) [379,380], fluperlapine (Sandoz) [380] and rilapine (Knoll Pharmaceuticals) [380]. However similar efficacy against negative symptoms and neuroleptic-induced extrapyramidal side effects has also been claimed for setoperone [381], risperidone [372] and melperone (Pharmacia) [382-384] while preclinical evidence suggests

that amperozide (Pharmacia) [385-387] is also atypical. All of these drugs have moderate or, in the case of amperozide and melperone, submicromolar affinities for the 5-HT_{1C} site [16,379,380]. Clearly no correlation can exist between 5-HT_{1C} receptor affinity and atypical antipsychotic properties. However, all the above compounds also have considerable affinity for the 5-HT_2 receptor [16,379,380] with tiosperone, rilapine, risperidone, setoperone, amperozide and melperone having between twenty- and one hundred and sixty-fold selectivity for the site [16,379,380], although tiosperone was not selective in the study of Canton *et al.* [379]. Hence 5-HT_2 receptor antagonism is much more likely to be the determinant of an atypical antipsychotic profile, although this does not account for the absence of such properties from chlorpromazine, spiperone and loxapine – all of which have high affinity for both 5-HT_2 and dopamine D_2 sites [380]. As 5-HT_{1C} receptors do not seem to be important in the action of antipsychotic drugs the induction of psychotic symptoms by mCPP is either secondary to anxiogenesis or mediated by properties unrelated to 5-HT_{1C} receptors. Such an effect may be observed by the drugs antagonist efficacy at 5-HT_2 receptors (Table 2).

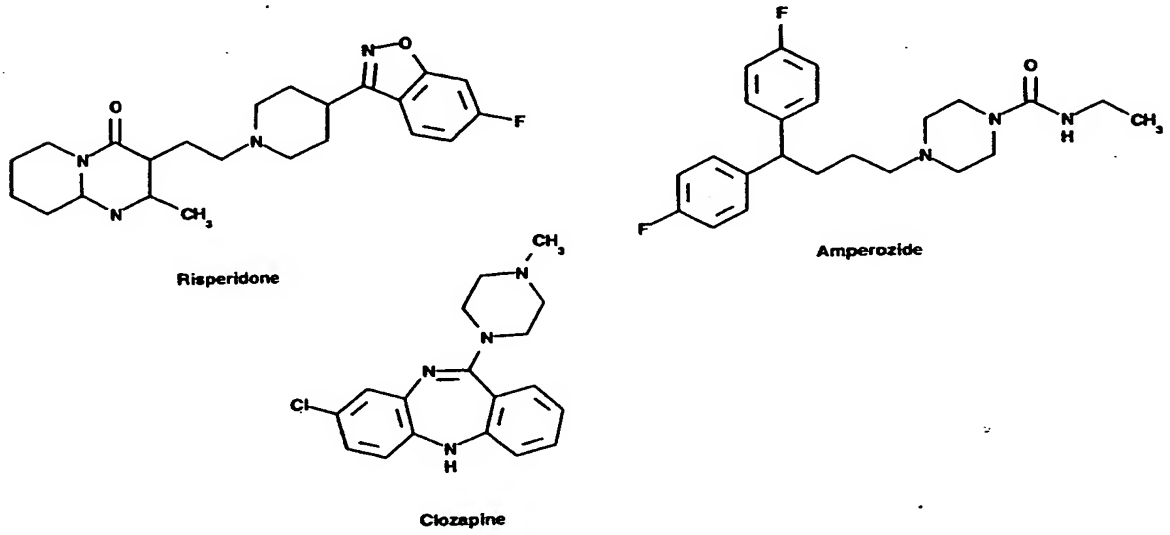


Figure 3: Antipsychotic agents

Autism

Autistic disorder is a syndrome originating in early childhood. It affects two to five children in every million, and is characterised by prominent distortions in social, linguistic and cognitive development. Pervasive lack of interest in others, and unresponsiveness to them, are essential features of the disorder.

Autistic children who develop spoken language often exhibit abnormal speech patterns including senseless or compulsive repetition of words heard (echolalia). Motor stereotypes such as hand flapping are common, as are self-abusive behaviours like head banging. Resistance to change is also characteristic. In the 1960s the syndrome was often described as early schizophrenia.

One prominent feature of autism is the presence of elevated plasma levels of 5-HT, which positively correlat with the cognitive, behavioural and motor deficits of subjects [388]. Studies of treatments designed to lower plasma 5-HT levels were therefore initiated. Early studies with fenfluramine, which is known to reduce brain 5-HT levels after chronic administration [389], reported dramatic effects in three autistic children [390]. However later studies have largely

found no effect of the drug on IQ or maladaptive behaviour and only a slight improvement in apparent developmental age [391]. The non-specific 5-HT antagonist, methysergide [16], was also without significant effect [392]. There is thus little evidence to support a role for 5-HT_{1C} receptor ligands in this disorder at the present time.

Table 6: Affinity of typical and atypical antipsychotic drugs for 5-HT_{1C} and 5-HT_2 receptors

Compound	pK_i 5-HT_{1C}	pK_i 5-HT_2	Selectivity for 5-HT_2 over 5-HT_{1C}	Class
Loxapine	9.4	8.7	4.7	Typical
Clozapine	8.1	8.3	1.4	Atypical
	8.1[a]	7.6[a]	0.3	
Tiosperone	8.0	10.2	153	Atypical
	7.6[a]	8.5[a]	7.9	
Fluperlapine	7.7	8.1	2.3	Atypical
Rilapine	7.6	9.1	29	Atypical
Chlorpromazine	7.6	8.7	13.5	Typical
	7.9[a]	8.1[a]	1.7	
Risperidone	7.5	9.7	160	Atypical
	7.5[a]	9.2[a]	49	
Setoperone	7.3[b]	8.6[b]	20	Atypical
Spiperone	6.0	9.4	2417	Typical
	6.0[a]	8.8[a]	631	
Amperozide	5.9	7.9	100	Atypical
Melperone	5.9	7.5	42	Atypical

All data from [380] except:
[a] Ref [379] [b] Ref [16]

Pain

5-HT_{1C} receptors have recently been identified in the spinal cord [393]. Iontophoretic administration of mCPP to dorsal horn nociceptive neurons located within the spinal cord is inhibitory [394]. Systemic administration of mCPP and TFMPP to spinal rats dose-dependently inhibited sensitivity to noxious stimuli which induce the ventroflexion withdrawal reflex [395]. This indicates a spinal or subspinal site of action. The pharmacology of these responses has not been investigated but 5-HT_{1C} receptor medication of antinociception was suggested by McKearney *et al.* [396]. In this study MK 212, mCPP and TFMPP all increase the shock intensity tolerated by monkeys. This effect was blocked by methysergide a non selective 5-HT_{1C} receptor antagonist (Table 1), but not by the selective 5-HT_2 receptor blockers ketanserin or pirenperone. Little human data exists, but, in contrast to the above, ritanserin was reported to increase subjective path thresholds [397]. This effect was modest however and might be related to the migraine prophylactic properties of the drug.

Priapism

MCPP, TFMPP or MK 212 administration causes penile erections in rats. MCPP-induced erections were antagonised by the 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin and ritanserin (Table 3, [231]) all of which have high affinity for the 5-HT_{1C} site [16]. The 50% inhibitory dose (ID_{50}) values of these drugs were higher than their equivalents against mCPP-induced hypophagia [66] but the rank order of potency was consistent in both paradigms. Ketanserin, the selective 5-HT_2 antagonist [16], also antagonised mCPP-induced penile erections but only at a relatively high dose [231] consistent with its weak affinity at the 5-HT_{1C} site [16] and its rank order of potency against mCPP-induced hypophagia [66]. The more selective 5-HT_2 receptor antagonist spiperone [16] was inactive [231]. Interestingly, the non-specific 5-HT_2/5-HT_{1C} agonist DOI (Table 3) only induced penile erections in the presence of specific 5-HT_2 receptor antagonists [231] suggesting an interaction between the two sites. MCPP also induced penile erection in rhesus monkeys which was blocked by metergoline [398]. The effect of mCPP may be mediated centrally as penile erections are seen in the rat after intraventricular administration of the 5-HT releasing agent fenfluramine [399], and the 5-HT precursor 5-hydroxytryptophan (5-HTP) is only effective when given with the peripheral decarboxylase inhibitor benserazide (Roche) [400].

In humans, priapism is a major disorder affecting ten million Americans [401]. Penile erection is caused by pooling of blood in the penile blood vessels. In priapism, prolonged stagnation of the pooled blood leads to a fall in oxygen content which increases its viscosity and results in fibrosis and impotence [402]. The condition is therefore considered a urological emergency. 30-50% of cases are drug induced, the most common agents being phenothiazines, butyrophenones, hypnotics (e.g. methaqualone), antihypertensives (eg phenoxybenzamine (SmithKline Beecham), prazosin (Pfizer), hydralazine), anticoagulants (heparin, warfarin) and miscellaneous agents such as ethanol, cannabis, phentolamine (Geigy) and testosterone [402]. Antidepressant therapy is also commonly associated with priapism, most notably with monoamine oxidase inhibitors such as phenelzine and the atypical antidepressant trazodone [402]. Since mCPP is a prominent metabolite of trazodone [56] this may explain its association with priapism, although this has not been reported as a consequence of mCPP administration to man [303]. MAOIs could act in a similar way by potentiating extracellular 5-HT. This may suggest a role for 5-HT_{1C} receptor antagonists in the prophylactic or acute treatment of this disorder, at least where caused by antidepressants.

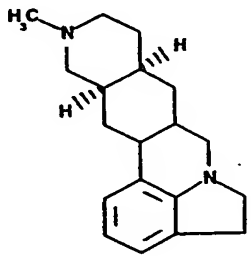
Altered intracranial pressure

The choroid plexus is the major site of formation of cerebral spinal fluid (CSF) in the brain [403,404]. Evidence suggests that 5-HT may control production of CSF, since administration of 5-HT and its precursor 5-HTP [405,406] are inhibitory. 5-HT may reach the choroid plexus from plasma, although concentrations are normally very low [407], or from mast cells found there [408,409]. Evidence also suggests direct serotonergic innervation. Thus moskowitz *et al.* [410] observed the presence of 5-HT that was sensitive to lesions of the raphe nuclei, the site of serotonergic neuronal cell bodies. Using a fluorescence technique that detected indoleamines, Napoleone *et al.* [411] reported that 5-HT neurons were located in the walls of the choroid blood vessels and were also sensitive to raphe cell body lesions. However not all studies have observed 5-HT innervation [412,413]. As has already been described (see above) the choroid plexus contains by far the highest concentration of 5-HT_{1C} receptors in any part of the body. It therefore seems likely that they mediate serotonergic control of CSF production as first suggested by Pazos *et al.* [6]. A recent study has shown that SCH 23390 (Schering Plough), a 5-HT_{1C} partial agonist [26,414] and dopamine D_1 antagonist [415], markedly

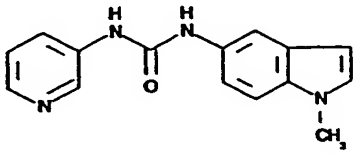
reduces CSF production in rats [416]. Since dopamine D_1 sites are not found in the choroid plexus [415] this effect is probably 5-HT_{1C} receptor mediated. These findings therefore suggest that 5-HT_{1C} receptor agonists may be of use in the treatment of patients with increased intracranial pressure such as those with mass lesions, head trauma, acute or hydrocephalus, or pseudotumour cerebri.

Conclusion

5-HT_{1C} receptor antagonists may have therapeutic applications in a number of areas. This possibility rests principally on the reported effects of the putative 5-HT_{1C} receptor agonist mCPP and of the non-specific 5-HT_2/5-HT_{1C} receptor antagonists ritanserin and mianserin as opposed to those of the selective 5-HT_2 receptor antagonist ketanserin. Unfortunately ketanserin is not entirely selective, possessing significant affinity for α_1 adrenergic receptors [250], a problem also seen with the newer selective 5-HT_2 receptor antagonist RP 62203 (Rhone Poulenc) [17]. Spiperone, which has proved of great value in defining 5-HT_{1C} functions *in vitro* due to its one thousand-fold selectivity for the 5-HT_2 site, is of little use *in vivo* because of its dopamine D_2 receptor antagonist properties. Similarly cisapride (Janssen) has one thousand-fold selectivity for the 5-HT_2 site but is also a potent 5-HT_3 antagonist and 5-HT_4 agonist [417]. Clarification of the therapeutic potential of 5-HT_{1C} receptor modulation should be considerably advanced by the recent development of selective 5-HT_{1C} receptor antagonists by both SmithKline Beecham [500] and Sandoz [501] (Figure 4) and the selective 5-HT_2 receptor antagonists RP 62203 [17] and MDL 101151 and its (+) isomer MDL 100907 which both have two hundred- to five hundred-fold selectivity for the 5-HT_2 site [418]. However it is also dependent on the pharmacological arguments advanced above, which are principally the result of animal data, being equally valid in humans. This cannot be taken for granted as mesulergine has fifty-fold lower affinity for the human than for the rat 5-HT_2 receptor. Thus in humans the drug would have selectivity for the 5-HT_{1C} site [21]. The probability that at least some of the above findings may be attributable to the action of drugs at the rat stomach fundus receptor (see section on receptor distribution), should it be found in human central tissue, cannot be excluded, despite preliminary evidence to the contrary [53,54]. In particular mCPP acts as a weak partial agonist of the rat stomach fundus [48,419] while most 5-HT_2/5-HT_{1C} receptor antagonists, but not specific 5-HT_2 receptor antagonists, are also antagonists of this site [48]. However current evidence strongly favours a therapeutic role for 5-HT_{1C} receptor ligands in at least some of the indications advanced in this review. Chronic treatment with selective 5-HT reuptake inhibitors is the current therapy of choice in many of these indications (OCD, alcoholism, depression, bulimia) and may become more widely used in others (panic disorder, obesity, migraine). Fluoxetine, the most widely studied drug in this class, is associated with significant side effects (insomnia, nausea, asthenia, tremor and sweating) [79] and may be associated with heightened risk of suicide in depressives [421-423] although these effects have not been reported for other 5-HT reuptake inhibitors. Furthermore, the reuptake inhibitors all require two or more weeks administration for effect. Should down regulation of 5-HT_{1C} receptors be their mode of action, the magnitude of this effect is unlikely to be as pronounced as that caused by an antagonist. Specific 5-HT_{1C} ligands may therefore offer advantages both in the speed of onset of action, efficacy, and side effect profile. Finally, it is conceivable that subtypes of the 5-HT_{1C} receptor may exist, although, with the exception of the rat stomach fundus receptor, there is no evidence of this at present. This might allow differentiation of the anxiogenic and other properties of 5-HT_{1C} receptor agonists facilitating their clinical use.



Sandoz



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SmithKline Beecham

Figure 4: Novel selective 5-HT_{1C} receptor antatagonists

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• = of interest •• = of considerable interest

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5-HT_{1C} receptors and their therapeutic relevance

GA Kennett

SmithKline Beecham, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, UK

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Introduction

Considerable advances have been made in the understanding of 5-hydroxytryptamine (5-HT) receptor pharmacology in the last decade. In 1979 the existence of more than one 5-HT receptor binding site was recognised for the first time when [^{3}H]lysergic acid diethylamine (LSD) binding in the rat cortex was found to contain 5-HT and spiperone (Janssen, Figure 1) sensitive components [1]. The 5-HT sensitive component was described as 5-HT_1 and the spiperone sensitive portion 5-HT_2. Subsequently Pedigo *et al.* [2] showed that at least two 5-HT_1 receptors existed, since high affinity [^{3}H]5-HT binding was partially displaced by spiperone. These putative receptor subtypes were termed 5-HT_{1A} (spiperone sensitive) and 5-HT_{1B} and can be more specifically labeled by [^{3}H]8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT) [3,4] and [^{125}I]iodocyanopindolol [5] respectively. Subsequently 5-HT_{1C} [6] 5-HT_{1D} [7], 5-HT_{1E} [8], 5-HT_3 [9,10] and 5-HT_4 [11] receptors have been identified.

The 5-HT_{1C} receptor

5-HT_{1C} receptor binding studies

One area found to contain 5-HT_1 binding sites by autoradiographic studies was the rat choroid plexus [12]. However these '5-HT_1' receptors were found to bind [^{3}H]mesulergine (Sandoz, Figure 1), a putative 5-HT_2 receptor ligand [13], but not the 5-HT_2 specific ligand [^{3}H] ketanserin (Janssen, Figure 1) [14,15]. The 5-HT_{1A} ligand 8-OH-DPAT and 5-HT_{1B} ligand RU 24969 (Roussel UCLAF) also failed to displace [^{3}H]mesulergine binding from this site which was therefore termed the 5-HT_{1C} receptor [6]. The pharmacology of this receptor has a considerable similarity to that of the 5-HT_2 receptor. Thus most 'classical' 5-HT_2 receptor antagonists such as mianserin (Organon, Figure 1) and methysergide (Sandoz), are unable to discriminate between the two sites. Exceptions include ketanserin (Janssen, Figure 1), altanserin (Janssen), pirenperone (Janssen), and spiperone, all of which show selectivity for the 5-HT_2 receptor [16] as do two recently developed compounds RP 62203 (Rhone Poulenc, Figure 1) [17] and SR 46349B (Sanofi) [18] (Table 1). 5-HT_2 receptor agonists are also largely non-selective; indeed only a few compounds, whether agonist or antagonist, show selectivity for the 5-HT_{1C} over the 5-HT_2 site (Table 1). These include 1-methyl 5-HT (one hundred-fold selective), MK 212 (Merck Sharp & Dohme, Figure 2; fifty-fold selective), (+)3-(2-aminopropyl)benz[e]indole hydrochloride (thirty-three-fold selective) [19], 1-naphthyl piperazine (1-NP) (ten-fold selective), 1-(3-chlorophenyl) piperazine (mCPP, Figure 2; ten-fold selective) and LY 53857 (Lilly; six-fold selective). 5-HT_{1C} receptors have been pharmacologically characterized in pig and human choroid plexus tissue and rat cortex. There were only minor differences in the affinities of the thirteen compounds tested [20].

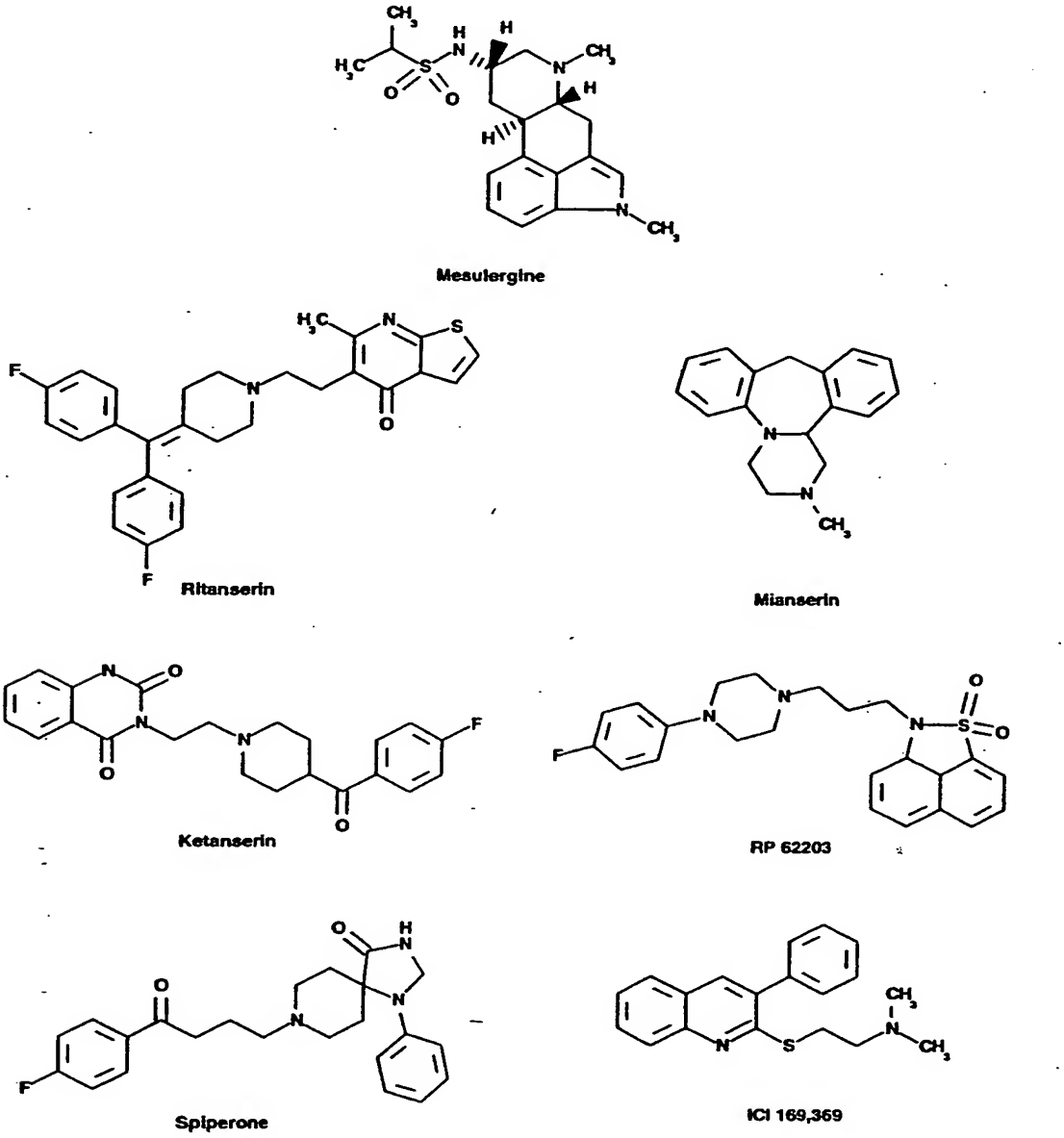


Figure 1: 5-HT_{1C}/5-HT_2 receptor antagonists

Several non-selective 5-HT_2/5-HT_{1C} receptor antagonists have been used clinically and many of the arguments advanced in the present review are based on their actions. Of these ICI 169,369 (Figure 1) and ICI 170,809 have the 'cleanest' profile. ICI 169,369 has thirteen-fold selectivity over the adrenergic α_1 receptor (Table 1). ICI 170,809 has twenty-fold higher affinity for 5-HT_{1C} site over the dopamine D_2 site and sixty-three-fold selectivity over the adrenergic α_1 receptor and one hundred-fold higher affinity for 5- HT_{1C} over the histamine H_1 site (Table 1). Ritanserin (Figure 1) has also been widely used clinically but has only three-fold selectivity for the 5-HT_{1C} over the H_1 receptor and only ten-fold over the adrenergic α_1 site. It also has high affinity for dopamine D_2 receptors (Table 1). Lastly mianserin is equipotent at 5-HT_{1C}, 5-HT_2 and H_1 receptors, has six-fold selectivity over 5-HT_3 and sixteen-fold selectivity over adenergic α_2 sites (Table 1). Clearly none of the above drugs is an ideal tool for the study of 5-HT_{1C} receptor function.

Even fewer agonists have been used, but one, mCPP, is discussed in some detail later. One problem with the interpretation of human data derived from the use of these drugs is that their affinities for human receptors may differ from their rat equivalents. One example of this is the fifty-fold higher affinity that mesulergine has for rat as opposed to human 5-HT_2 receptors [21]. This may give mesulergine a fifty-fold greater affinity for the 5-HT_{1C} over the 5-HT_2 receptor in humans. In the same study ritanserin had a seven-fold lower affinity for rat than for human 5-HT_2 sites.

Table 1: Affinity values of 5-HT_{1C} receptor antagonists for 5-HT, adrenergic α_1 and α_2, dopaminergic D_2 and histamine H_1 receptors in mammalian brain membranes.

Drug	5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_{1D}	5-HT_2	5-HT_3	α_1	α_2	D_2	H_1
1-NP	7.2	6.6	8.3	7.8[b]	7.2	6.9	-	-	-	-
LY 53857	6.4	5.5	8.1	-	7.3	7.5[f]	-	-	-	-
Mesulergine	6.2	4.9	8.8	5.2	8.4	-	5.3[b]	6.1[b]	6.8[b]	5.2[b]
ICI 169,369	5.3	-	8.0[c]	6.3	7.8[d]	6.0[c]	6.2[d]	5.9[d]	6.9[d]	6.0[d]
ICI 170,809	< 6.0[g]	-	8.3[f]	-	9.1[g]	-	7.0[g]	-	6.1[g]	6.3[g]
Metergoline	8.1	7.4	9.2	8.3	9.0	-	7.0[a]	6.0[a]	7.2[a]	5.7[a]
Ritanserin	5.2	< 4.0	8.9	5.8	8.8	5.6[g]	7.9[g]	7.1[g]	7.5[g]	8.4[g]
Methysergide	7.6	5.8	8.6	8.4	8.6	4.5	5.2[a]	5.2[a]	6.3[a]	<6.0[a]
Mianserin	6.0	5.2	8.0	6.4	8.1	7.2	6.6[a]	6.8[a]	5.8[a]	8.3[a]
SR 46349B	4.9[i]	4.8i	6.9[i]	< 6.0[i]	8.2[i]	-	5.5[i]	6.0[i]	< 6.0[i]	5.3[i]
RP 62203	7.1[g]	< 6.0[g]	8.5[f]	-	9.9[g]	5.2[g]	8.4[g]	< 6.0[g]	6.4[g]	7.3[g]
Setoperone	5.6	5.3	7.3	-	8.6	-	-	-	-	-
Pirenperone	5.9	5.3	7.3	-	8.8	-	-	-	-	-
Altanserin	5.6	6.0	6.9	-	8.6	-	-	-	-	-
Cisapride	5.7	5.2	6.3	5.3	8.1	-	-	-	-	-
Ketanserin	5.9	5.7	7.0	6.0	8.9	3.6	7.5[a]	< 6.0[a]	6.3[a]	7.7[a]
Spiperone	7.2	5.3	5.9	5.3	8.8	3.6	-	-	-	-

Data taken from [16] or [423] except:

[a] Ref [15] [b] Ref [62] [c] Ref [100]
[d] Ref [250] [e] Ref [103] [f] Wood MD, personal communication
[g] Ref [17] [h] Ref [13] [i] pIC_{50} values from [18]

The 5-HT_{1C} receptor secondary messenger system

Palacios *et al.* [22] reported that activation of 5-HT_{1C} in the pig choroid plexus had no effect on adenylate cyclase activity. However 5-HT was found to cause the stimulation of phospholipase C and the breakdown of phospholipids in homogenates of this tissue [23], actions usually associated with the release of Ca^{2+} ions from the intracellular stores [24,25]. This effect was potently inhibited by the non-selective 5-HT_{1C}/5-HT_2 receptor antagonist mianserin but only by high concentrations of the selective 5HT_2 receptor antagonist [16] ketanserin and spiperone [23], suggesting 5-HT_{1C} receptor mediation. Subsequently Hoyer *et al.* [26] correlated the potency of twelve agonists and fourteen antagonists in inducing or inhibiting 5-HT-induced phosphoinositide (PI) hydrolysis in choroid plexus cells, with their

affinities for the 5-HT_{1C} receptor. Since 5-HT_2 receptors are also coupled to a PI hydrolysis secondary messenger system this is another common feature of the two receptors.

5-HT_{1C} receptor stimulation may also result in activation of Cl^- channels. Application of 5-HT to Xenopus oocytes injected with rat brain or choroid plexus messenger ribonucleic acid (mRNA) causes PI hydrolysis and increased intracellular Ca^{2+} levels. This in turn was shown to cause the opening of Ca^{2+}-dependent Cl^- channels [27-30]. The pharmacology of Cl^- ion channel activation by 5-HT in this system is most consistent with 5-HT_{1C} receptor mediation [28,29]. However there are several discrepancies such as the relatively high affinity of ketanserin and low affinity of cyproheptadine (Merck Sharp & Dohme) and mesulergine compared to that determined by receptor binding [16,28]. In Xenopus oocytes expressing mRNA from rat brain the effect of 5-HT on Cl^- currents was mimicked by the intracellular application of guanosine triphosphate α (GTP)-γ-S. Both effects were blocked by injection of the Ca^{2+} chelator ethylene glycol-bis(β-aminoethyl ether) N,N,N,N-tetraacetic acid (EGTA). The effect of 5-HT was also blocked by pertussis toxin which was shown to promote the adenosine diphosphate (ADP)-ribosylation of a GI-protein [31]. This data suggests that a Ca^{2+} dependent Cl^- ion channel is activated via a G-protein stimulation of phosphoinositide hydrolysis. 5-HT mediated stimulation of ion channels has also been observed in oocytes expressing mRNA from both human brain [27] and rat small intestine [32], although no pharmacological analysis was made. It remains to be seen whether 5-HT_{1C} receptors in the brain are coupled to Cl^- channels, or whether this coupling is artificially created by the expression of mRNA in an alien cell and its endogenous inositol phospholipid signalling system.

Evidence from Xenopus oocytes injected with both rat brain 5-HT_{1C} receptor and K^+ channel mRNA, suggests that 5-HT_{1C} receptors may modulate the function of K^+ channels. Thus in the presence of EGTA to suppress Cl^- ion channel activation, 5-HT causes an inward current, not found in oocytes injected with either mRNA alone [33], which is due to the closing of a class of K^+ channels [34,35].

5-HT_{1C} receptor molecular biology

The 5-HT_{1C} receptor was first cloned by Lubbert *et al.* [29] from rat choroid plexus tissue. The method used involved isolating rat choroid plexus mRNAs, fractionating them by gel electrophoresis and expressing them in Xenopus oocytes where stimulation of the 5-HT_{1C} receptor, formed from the desired mRNA, results in Cl^- ion channel opening. The mRNA thus identified had a molecular weight of 5000 daltons. Later Julius *et al.* [36] published the amino acid sequence of this receptor which contained 460 residues. The sequence revealed seven regions of hydrophobicity each of 20-30 amino acids. These regions would be expected to associate with the hydrophobic lipid membrane to form helical transmembrane domains. This arrangement is common to all members of the G protein-coupled receptor family of membrane proteins which include the 5-HT_2, 5-HT_{1A}, adrenergic β receptor and muscarinic acetylcholine receptors amongst others. The family is so called because the response to receptor activation is indirectly mediated by a class of GTP-hydrolysing enzymes allosterically coupled to the receptor. Thus receptor stimulation activates a G protein which in turn acts upon the cellular system [37]. A more recent study has suggested that the 5-HT_{1C} receptor in rat and mouse have an eighth transmembrane domain not found in other members of the G protein-coupled family [38]. Human 5-HT_{1C} receptor sequences have also been recently reported [39]. Both mouse and human sequences are very similar to the rat, the mouse amino acid sequence having 97% [38] and human 90% [39] homology. These small differences have not yet been observed to have great pharmacological significance.

One observation from the sequencing of the 5-HT_{1C} receptor was its resemblance to the 5-HT_2 receptor. In rat the overall homology is 51% as opposed to 35% for the 5-HT_{1A} receptor. When the seven transmembrane domains are compared this rises to 79% homology for the 5-HT_2 receptor [40]. In humans total 5-HT_2 and 5-HT_{1C} gene sequence homology was 50% and in transmembrane domains 80% [39].

It is of some interest that the 5-HT_{1C} receptor gene is located on the X chromosome, unlike 5 HT_2 or 5-HT_{1A} receptors [38]. This suggests that it may be involved in the effects of 5-HT on sexual differentiation [41].

5-HT_{1C} receptor distribution

Autoradiographic studies using [^{3}H]mesulergine in rat brain have demonstrated very high densities of 5-HT_{1C} receptor binding sites in the choroid plexus with roughly ten-fold lower densities in the hippocampus CA1 region, substantia nigra, globus pallidus, layer III of the cerebral cortex, olfactory cortex, lateral amygdaloid nucleus and thalamus [42]. This distribution is paralleled in mice [43]. A more detailed study of the human brain has also revealed a similar distribution. Here low levels were widely distributed in the following rank order of density: hypothalamus ventromedial nucleus > globus pallidus > hippocampus CA1 and CA3 > substantia nigra, nucleus accumbens, putamen > amygdala > thalamus. Other regions contained even lower densities [20,44].

One problem with the mapping of 5-HT_{1C} receptors is the high level of non-specific binding encountered with [^{3}H]mesulergine [44]. The mapping of 5-HT_{1C} mRNA is more specific and has allowed improved accuracy. Several studies have been conducted. In general these have confirmed receptor binding distributions. However some discrepancies have emerged, particularly the relatively high densities of mRNA in the septum, lateral habenula and subthalamic nucleus which are not matched by high levels of binding [43,45]. These may suggest differences in regional receptor turnover rates or reflect transport of mRNA from the cell body site of synthesis to the site of expression. Some discrepancies may be due to experimental differences. Thus Hoffman & Mezey [45] report high 5-HT_{1C} mRNa levels in rat dentate gyrus not seen by Molineaux *et al.* [46] or Mengod *et al.* [43], while Molineaux *et al.* [46] report high levels in the hippocampal CA1 region which were not seen by Hoffman & Mezey [45] or Mengod *et al.* [43].

The existence of 5-HT_{1C} receptors outside the brain has yet to be demonstrated. Only one model has been proposed: mediation of 5-HT-induced contractions of the rat stomach fundus [47]. This rests on the antagonist potency in this model of the older 5-HT_{1C}/5-HT_2 receptor antagonists such as mianserin, methysergide and pizotifen (Sandoz) but not specific 5-HT_2 receptor antagonists [48,49]. However there are a number of differences. Yohimbine and rauwolcine, which are also potent antagonists of 5-HT in the fundus [48], have little affinity for the 5-HT_{1C} receptor [16]. Also many 5-HT_{1C}/5-HT_2 receptor antagonists act as non-surmountable antagonists [48] making predictions of affinity difficult. Furthermore 5-HT stimulation of the fundus appears not to cause PI hydrolysis [50]. No 5-HT_{1C} mRNA was detected in the tissue [51] while extracted mRNA expressed in Xenopus oocytes inhibited cyclic adenosine monophosphate (CAMP) formation [52]. Recently Foquet *et al.* [53] reported that the rat stomach fundus gene is closely related to, but structurally distinct from, the 5-HT_2 and 5-HT_{1C} receptor genes. This receptor was not observed in brain tissue in further studies by this group [54].

The expression of 5-HT_{1C}-like receptors from rat small intestine mRNA injected into oocytes [32] suggests that peripheral 5-HT_{1C} receptors may exist. 5-HT_{1C} receptor mediation of penile erections in rats, however, is likely to be centrally mediated [55].

MCPP - a putative 5-HT_{1C} agonist

MCPP is a metabolite of the widely prescribed antidepressant trazodone (Bristol-Myers Squibb) [56]. For this reason it has been considered ethical to administer the drug to humans. MCPP has principally been considered a 5-HT_{1B} agonist since it reduces 5-HT release in brain slices [57] and was observed to displace supposed 5-HT_{1B} receptor binding [58], although the preparation used would have contained 5-HT_{1C} receptors as well. In 1988 two prominent behavioural effects of mCPP, hypolocomotion [59] and hypophagia [60], were reported to be caused by 5-HT_{1C} receptor stimulation. This was consistent with receptor binding studies in which the drug had at least ten-fold selectivity over other 5-HT receptor subtypes including 5 HT_{1B} sites (Table 2). It was also consistent with the ability of mCPP to stimulate PI hydrolysis in the rat choroid plexus [61]. In this paradigm mCPP is reported to act with 65 to 90% of the efficacy of 5-HT whether rat [61] or pig [62,63] tissue is used, although both preparations have little receptor reserve [63,64]. MCPP's selectivity as a 5-HT_{1C} agonist is enhanced by its actions as a silent antagonist at cortical 5-HT_2 receptors mediating PI hydrolysis [61], in the 5-HT_2-mediated head twitch model in rats [65, 66] and in the 5-HT_2-mediated rat jugular vein model [67]. It is also an antagonist of rat vagus nerve [10] and rat cardiac [68] 5-HT_3 receptors. Against bovine 5-HT_{1D} receptors, Schoeffter & Hoyer [62] reported that it was a weak (30%) partial agonist with an estimated pK_B of 5.1. This was somewhat less than its binding affinity for the site; pK_I = 5.8–5.9 (Table 1). Recently two 5 HT_{1D} receptor subtypes have been identified 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ [69]. The affinity of mCPP for cloned human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors is reported to be 6.6 and 6.4 respectively [69]. The slightly higher affinity of mCPP for these cloned human 5-HT_{1D} receptors may reflect species differences or conceivably an artifact. MCPP has little affinity for 5-HT_{1E} or 5-HT_4 receptors.

The ten-fold selectivity of mCPP for 5-HT_{1C} over 5-HT_{1B} receptors evidenced by binding studies was not observed in a comparision of its efficacy in stimulating their respective secondary messengers [62] (Table 2) although selectivity over 5-HT_{1A}, 5-HT_{1D} and 5-HT_2 receptors was largely maintained. This was due to a large proportion of agonists tested having pEC_{50} values in the 5-HT_{1C} PI hydrolysis test roughly ten-fold lower than their binding affinities [26,62]. Since the degree of amplification needed to evoke a physiological or behavioural response in the different systems is unknown the relevance of this finding it unclear. Furthermore its relevance to mCPP's effects in man is also unclear. While 5-HT_{1B} receptors are not widely distributed in human tissue [44], a species homologue, the 5-$HT_{1D\beta}$ receptor, is found [69]. At the present time no data as to the effects of mCPP on this receptor's secondary messenger systems has been reported.

MCPP has also been reported to have some affinity for the adrenergic α_2 receptor (pK_D = 6.2) [70]. This is approximately forty-fold less potent than its affinity for 5-HT_{1C} receptors [62], although whether mCPP acts as an agonist or antagonist at these sites is unknown. Another ambiguity is the reported release of 5-HT *in vitro* by mCPP [71]. The importance of this effect has yet to be clarified but implies that intact presynaptic serotonergic function would be necessary to sustain an effect of mCPP mediated in this way. MCPP has very weak affinity for the adrenergic α_1 and β receptors, and for the dopamine D_2, muscarinic and benzodiazepine receptors [72].

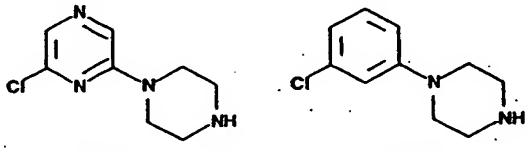


Figure 2: 5-HT_{1C} agonists

Table 2: Profile of the *in vitro* actions of mCPP

Receptor	Affinity of mCPP		Functional model		
	Rat or Pig (pK_I or pK_D)	Human (pIC_{50})	Model	pEC_{50} (pK_B or pA_2)	Efficacy (%)
5-HT_{1A}	6.6[a]	6.4[b]	Adenylate cyclase	5.9	40[c]
5-HT_{1B}	6.5[a]		Adenylate cyclase	6.5	60[c]
5-HT_{1C}	7.8[a]		Phosphoinositide hydrolysis	6.9	65[c]
	7.4[d]			7.1	90[d]
5-HT_{1D}	5.8[a]	5.9[b]	Adenylate cyclase	5.1	30[c]
5-$HT_{1D\alpha}$	6.6[i]				
5-$HT_{1D\beta}$	6.4[i]				
5-HT_{1E}	5.0[i]				
5-HT_2	6.7[a]	6.6[b]	Phosphoinositide hydrolysis	6.1**	0[c]
5-HT_3	7.0[a]		Vagus nerve	6.6***	0[b]
5-HT_4	5.0[i]				
α_1 adrenoceptor		5.5[b]			
α_2 adrenoceptor	6.2[f]	6.2[b]			
β adrenoceptor		5.6[b]			
Dopamine D_1		5.1[b]			
Dopamine D_2		5.0[b]			
Benzodiazepine	< 4.0[b]				
5-HT reuptake	< 4.0[b]				
5-HT release	0.1-1mM*[g]				

* Minimum effective dose
** pK_I
*** pA_2

Data taken from:

[a] [16] [b] [72] [c] [62] [i] [AM Brown, personal communication]
[d] [63] [e] [61] [f] [70]
[g] [71] [h] [10] [i] [69]

In conclusion, mCPP is a 5-HT_{1C} receptor agonist and may have some selectivity for the site. In humans this selectivity may be promoted by the apparent absence of the 5-HT_{1B} receptor although this may be offset by the higher affinity of the drug for cloned human 5-$HT_{1D\alpha}$ and 5-

$HT_{1D\beta}$ receptors [44]. The effects of mCPP in man have greatly contributed to perceptions of the utility of 5-HT_{1C} receptor ligands.

Table 3: Behavioural effects of mCPP in rats: models of 5-HT_{1C} receptor function?

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Reference]
Hypolocomotion	Metergoline	1-5	5-HT_1, 5-HT_2	Blocks[b,c] [59,229,235,426,427]
	Methysergide	5-10	5-HT_1, 5-HT_2	Blocks[b,c] [427]
	Mianserin	2	5-HT_{1C}, 5-HT_2, α_2	Blocks[b,c] [59,427]
	Cyproheptadine	2	5-HT_{1C}, 5-HT_2, H_1	Blocks [59] / No effect[b] [427]
	Mesulergine	0.5-4	5-HT_{1C}, 5-HT_2	Blocks[b] [427]
	Ketanserin	0.2-1	5-HT_2	No effect[c] [59,426]
	Ritanserin	0.1-2	5-HT_2	No effect[b] [59,426,427]
	Spiperone	0.01-0.05	5-HT_2, D_2	No effect?[b] [427]
	Cyanopindolol	0.2-8	5-HT_{1A}, 5-HT_{1B}, β	No effect[b] [59,427]
	Pindolol	2	5-HT_{1A}, 5-HT_{1B}, β	No effect[c] [59]
	Propranolol	5-16	5-HT_{1A}, 5-HT_{1B}, β	No effect[c] [59] / Potentiates [235]
	ICS 205,930	1	5-HT_3	No effect [59,427]
	MDL 72,222	0.5	5-HT_3	No effect [426]
	Idazoxan	1	α_2	No effect [59,427]
	PCA	Chronic	5-HT lesion	Blocks [427]
	PCPA	Chronic	5-HT depletion	No effect [Unpublished observation]
Hypophagia	Metergoline	1-5	5-HT_1, 5-HT_2	Blocks[d] [60,428,429]
	Mianserin	2-5	5-HT_{1C}, 5-HT_2 α_2	Blocks[d] [60]
	Cyproheptadine	10	5-HT_{1C}, 5-HT_2 H_1	No effect [60]
	Mesulergine	0.2	5-HT_{1C}, 5-HT_2	Blocks[d] [60]
	Ketanserin	0.2	5-HT_2	No effect[e] [60]
	Ritanserin	0.6	5-HT_2[a]	No effect[e] [60]
	Cyanopindolol	8	5-HT_{1A}, 5-HT_{1B} β	Blocks[e] [60]
	Propanolol	16	5-HT_{1A}, 5-HT_{1B} β	Blocks [60]
	ICS 205,930	1	5-HT_3	No effect [60]
	Idazoxan	1	α_2	No effect [60]
	Median Raphe lesion		Lesion	No effect [428]

Table 3: (cont.)

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Reference]
Penile Erection	Metergoline	0.02-0.2	5-HT_1, 5-HT_2	Blocks [231]
	Mianserin	0.02-0.2	5-HT_{1C}, 5-HT_2 α_2	Blocks [231]
	Cyproheptadine	0.1-1.0	5-HT_{1C}, 5-HT_2 H_1	Blocks [231]
	Mesulergine	0.02-0.2	5-HT_{1C}, 5-HT_2	Blocks [231]
	Ketanserin	0.5-1.0	5-HT_2	No effect [231]
	Ritanserin	0.1-0.5	5-HT_2 [a]	Blocks [231]
	Spiperone	0.1-1.0	5-HT_2, D_2	No effect [231]
	GR 38032F	1-10	5-HT_3	No effect [231]
Hyperthermia	Metergoline	0.5	5-HT_1, 5-HT_2	Blocks [233]
	Ritanserin	0.6[a]	5-HT_2	No effect [233]
	Pindolol	4	5-HT_{1A}, 5-HT_{1B} β	No effect [233]
	Propanolol	6	5-HT_{1A}, 5-HT_{1B} β	No effect [233]
Purposeless Chewing	Mianserin	1	5-HT_{1C}, 5-HT_2	Blocks [431]
	Ketanserin	5	5-HT_2	No effect [431]
	Spiperone	0.5	5-HT_2, D_2	No effect [431]
	ICS 205,930	10	5-HT_3	No effect [431]
	(–)Propranolol	20	5-HT_{1A}, 5-HT_{1B} β [f]	Blocks [431]

[a] Since the *in vivo* ID_{50} value for ritanserin against mCPP-induced hypophagia was 4.6 mg/kg *sc* [66], doses below this may be 5-HT_2 selective.

[b/c] Similar results obtained against TFMPP-induced hypolocomotion. Results from [b] [427] and [c] [229].

[d] Similar results obtained against TFMPP-induced hypophagia in freely feeding rats [430].

[e] Ketanserin 2.5 mg/kg partially blocked, cyanopindolol had no effect and ritanserin 0.5 and 1 mg/kg *ip* had an inverse dose related effect on TFMPP-induced hypopgagia [430].

[f] As (-)propranolol does not have pronounced specificity for 5-HT_{1A} and 5-HT_{1B} over 5-HT_{1C} sites [16], this dose may have blocked them all.

Possible therapeutic targets of 5-HT_{1C} receptor ligands:

Anxiety

Anxiety is widely observed in nearly all forms of mental illness. It is present in its purest form in anxiety disorders but is a noted feature of depression, schizophrenia and personality disorders. Four major types of anxiety have been characterised; generalised anxiety disorder (GAD), panic disorder with or without agorophobia, obsessive compulsive disorder (OCD), and other phobias. Several problems are associated with existing therapy. One of the most serious is the development of dependence in patients on long term benzodiazepine treatment. This leads to the induction of a marked anxiety on withdrawal [73]. Other problems include sedation and the interaction of this class of drugs with alcohol and barbiturates. Furthermore benzodiazepines are ineffective in the treatment of OCD [74], which only responds to chronic treatment with some antidepressants [75] and is then only partly effective. Chronic

antidepressant treatment is also efficacious in panic disorder [76-78]. However the side effect profile of this class of drugs (which includes anticholinergic, sedative and postural hypotensive effects for tricyclic antidepressants and hypotension and insomnia for monoamine oxidase inhibitors (MAOI)) has prevented their widespread use in these indications. Even the selective 5-HT reuptake inhibitor (SSRI) fluoxetine (Lilly) is associated with insomnia, nausea and asthenia [79].

Generalised anxiety disorder

Administration of mCPP to human volunteers caused anxiety [80-84]. In some subjects panic attacks were experienced [84,85]. The anxiogenic response to mCPP is accompanied by an increase of the stress sensitive hormones adrenocorticotrophic hormone (ACTH), cortisol and prolactin [80,86,87]. However there is some uncertainity over whether the hormonal changes are secondary to anxiety or not. Two studies of prolactin release suggest that it does follow peak anxiety [81,86] while one does not [84], although significant anxiety was not seen in this study.

MCPP administration to rats also induces anxiogenic-like responses in both the social interaction (SI) [88,89] and the elevated X-maze [Kennett, unpublished observations] models of anxiety, and decreases punished responding in a pigeon conflict model [90]. However in both the rat Geller-Seifter [91] and acoustic startle [92] models of anxiety the actions of mCPP were obscured by sedative or motor effects.

The anxiogenic response to systemic mCPP in the SI test was replicated after intra-hippocampal, but not intra-amygdaloidal, infusion [89]. This region has long been associated with the control of anxiety and is known to contain 5-HT_{1C} receptors [42,43,45,46]. The effect of mCPP, at least in the elevated X-maze, is not secondary to the release of 5-HT as it is not opposed by pretreatment with the 5-HT synthesis inhibitor p-chlorophenylalanine [Kennett, unpublished observations].

The pharmacology of the anxiogenic responses to mCPP in the rat SI and elevated X-maze tests is consistent with 5-HT_{1C} mediation. Thus in the SI test it is blocked by the non specific 5-HT_2/5-HT_{1C} receptor antagonists mianserin, cyproheptadine and metergoline (Farmitalia) (Table 1) but not by the selective 5-HT_2 antagonist ketanserin (Table 1) or by the 5-HT_{1A} and 5-HT_{1B} receptor antagonists [16] cyanopindolol (Sandoz) and (-)propranolol (ICI) [88]. The action of mCPP in the X-maze was similarly opposed by the non-selective 5-HT_2/5-HT_{1C} receptor blockers mianserin, LY 53857 and 1-NP [16], but not by the selective 5-HT_2 antagonists ketanserin and altanserin [16] nor by the 5-HT_{1A} and 5-HT_{1B} receptor blockers pindolol (Sandoz) [16] and cyanopindolol [Kennett, unpublished observations]. The effects of mCPP in both models was opposed by the benzodiazepine anxiolytic chlordiazepoxide (Roche) [88,93] reinforcing the interpretation that mCPP is anxiogenic. The anxiogenic effects of mCPP in both models were also attenuated by the 5-HT_3 receptor antagonists [16,94] ICS 205,930 (Sandoz) [88] and BRL 46470A (SmithKline Beecham) [93] in the SI and X-maze tests respectively. This is likely to be caused by the anxiolytic profile of these drugs [93,95]. Indeed mCPP might have more pronounced anxiogenic activity if it had less affinity for the 5 HT_3 site at which it is an antagonist (Table 1).

The results from rat models are consistent with the available clinical data. Thus the anxiogenic responses to mCPP have been reported to be blocked by the non-selective 5-HT_1 and 5-HT_2 receptor antagonists metergoline [85,96] and methysergide [85] and by the 5-HT_2/5-HT_{1C} receptor antagonist ritanserin (Janssen) [83]. This last report is of considerable interest, as

ritanserin has little affinity for other 5-HT receptor subtypes [16] and mCPP itself is a 5-HT_2 antagonist (see section on mCPP as a putative 5-HT_{1C} agonist).

The effects of antagonists on neuroendocrine responses to mCPP are similar. Metergoline and ritanserin both attenuate mCPP-induced prolactin secretion [83,87,96,97]. They also blocked the increase in cortisol [83,87,97]. Metergoline blocks the ACTH response as well [87]. Methysergide, however, was reported to block prolactin but not cortisol responses to mCPP [97].

Mediation of the anxiogenic effects of mCPP by 5-HT_{1C} receptor activation suggests that their blockade would be anxiolytic provided that some tone is exerted through the receptors under normal and/or anxiety provoking conditions. This hypothesis is supported by evidence from animal studies. In two recent studies [98,99], five non-selective 5-HT_2/5-HT_{1C} receptor antagonists, mianserin, 1-NP, ICI 169,369 (ICI), LY 53857 and pizotifen, (Table 1, [16,100]), were found to have anxiolytic-like actions in both the SI and Geller Seifter conflict tests. Compounds that did not share this property include: the selective 5-HT_2 antagonists ketanserin and altanserin, (Table 1); 5-HT_{1A} and 5-HT_{1B} receptor antagonists pindolol and cyanopindolol [16]; adrenergic α_2 receptor antagonist idazoxan (Reckitt and Colman) [101] or adrenergic α_2 antagonist and 5-HT_{1D} partial agonist yohimbine [101,102]; and H_1 antagonist mepyramine (May and Baker). The possibility of 5-HT_3 mediation of the effects is also unlikely as ICI 169, 369 [103] and LY 53857 (Table 1) have low affinity for this site, and 5-HT_3 antagonists are inneffective in the Geller-Seifter test [104,105]. Since the two tests have different motivational and aversive components the conclusion that these non-selective 5-HT_{1C} receptor antagonists are anxiolytic is strengthened. Similar findings have not been universally reported. The 5-HT_2/5-HT_{1C} receptor antagonist ritanserin, for instance, was inactive in one SI test [106], although the conditions used were inappropriate for the detection of anxiolysis [98]. The compound was active in one rat conflict procedure [107] but not in three others [108,109], although the paradigms used in the latter study were insensitive to benzodiazepines also. However, in the pigeon conflict test, claimed to be more sensitive to serotonergic drugs, ritanserin has shown an anxiolytic profile [90,109]. Mianserin, too, had no effect on SI where relatively high doses were used [110] but was active in the Geller-Seifter test when lower doses, similar to those of Kennett [98] or Kennett *et al.* [99], were used [111]. Another 5-HT_2/5-HT_{1C} receptor antagonist cyproheptadine [16] was also effective in some [112,113] but not all [108] conflict tests, while ICI 169,369 had some activity in the pigeon conflict test [114]. The non-specific 5-HT_1 and 5-HT_2 antagonists methysergide and metergoline [16] were not active in the SI test, albeit under different conditions [115], but were active in conflict tests [116-120]. The selective 5-HT_2 receptor antagonist ketanserin has also shown an anxiolytic profile in the pigeon conflict model [90]. This may reflect species differences in the 5-HT_{1C} receptor, or in the metabolism and disposition of ketanserin.

Another rat model claimed to be relevant to anxiety is the response to electrical stimulation of the periaqueductal gray (PAG). In humans this elicits unpleasant and fearful sensations [121] and in animals causes vigorous flight or defense reactions [122]. In this model mCPP acts as an anti-aversive agent; 5-HT_2/5-HT_{1C} antagonists mianserin, cyproheptadine and ritanserin as pro-aversive agents; and selective 5-HT_2 antagonists ketanserin, pirenperone and spiperone as anti-aversive agents [123]. Since mCPP is clearly anxiogenic both clinically and in other animal models the relevance of this paradigm is uncertain, but it may apply to a particular type of anxiety. Recently Beckett *et al.* [124] have reported mCPP to be pro-aversive when the PAG was chemically stimulated by homocysteic acid. This effect was blocked by mianserin.

The difference between these results and those obtained using electrical stimulation of the PAG may be due to the stimulation of fibres of passage by the latter technique.

Taken as a whole these results suggest that 5-HT_{1C} antagonists are anxiolytic in at least some animal models. This is consistent with reports of the clinical anxiolytic properties of mianserin [125–128] and the effectiveness of ritanserin in generalised anxiety disorder [129–131]. Metergoline, however, is not anxiolytic [75] and may be anxiogenic clinically [132]. This may reflect its non-specificity for 5-HT_1 subtypes [16] and possibly the different distribution of receptors in man and rat. It is of considerable interest that selective 5-HT_{1C} receptor antagonists have been claimed to possess anxiolytic activity, being active in the SI and Geller-Seifter test, in a recent SmithKline Beecham patent [500].

Panic Disorder

The administration of mCPP to normal volunteers evoked anxiety resembling panic attacks in some subjects [84,85]. In panic disorder patients, mCPP was found to induce panic attacks in roughly half of those treated. These were reportedly indistinguishable from those normally experienced [81,85,133–135]. The increase in anxiety and panic reported by these patients was also greater than that of healthy volunteers [85,133,134] although this did not reach significance in the study by Charney *et al.* [81]. However this group may have achieved a supramaximal response.

Neuroendocrine responses to mCPP in panic disorder patients followed a similar pattern. Thus Kahn *et al.* found that plasma cortisol responses to mCPP were enhanced [133], as were ACTH and prolactin in female, but not male panic disorder patients [136]. However cortisol, prolactin and growth hormone responses were not different from healthy volunteers in the study of Charney *et al.* [81] as observed for the anxiety response.

The above evidence has been used to argue the existence of hypersensitive 5-HT receptors in panic disorder. Since the anxiogenic effects of mCPP are probably 5-HT_{1C} receptor mediated (see above) these may be the hypersensitive 5-HT receptors in panic disorder. However the enhanced responses to mCPP could instead be secondary to hypersensitive anxiety mechanisms distal to 5-HT_{1C} receptors themselves. This view is supported by the ability of caffeine [135,137,138], yohimbine [139] and lactate [140], anxiogenic agents with differing modes of action to mCPP, to also induce a greater degree of anxiety in panic disorder patients, although not all induce robust increases in cortisol or prolactin [135]. The hypothesis may be further supported by the lack of clinical efficacy of the 5-HT_{1C} and 5-HT_2 receptor antagonist ritanserin in panic disorder [141] although an earlier open trial of the drug did suggest some benefit [142]. Furthermore the efficacy of tricyclic antidepressants [76] and the specific 5-HT reuptake inhibitor fluoxetine [77,78] after chronic administration may be mediated by down regulation of 5-HT_{1C} receptors (see section on depression).

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is characterised by obsessions (recurrent, intrusive thoughts) and compulsions (repetitive behaviours) such as ritualistic washing or checking which the patient recognises as senseless. The patients experience significant anxiety but the most common complication of primary OCD is depression [75]. OCD is refractory to benzodiazepine anxiolytics, despite reduced anxiety levels [74]. However chronic treatment with the antidepressant chlorimipramine (Geigy) [143,144] was found to ameliorate symptoms to a greater degree than other tricyclic and MAOI antidepressants [145]. Since chlorimipramine is a relatively selective 5-HT reuptake inhibitor [146] this suggested that a defective 5-HT

system might be involved, as did the effectiveness of treatment with the 5-HT precursor tryptophan [147] and the correlation of clinical efficacy of chlorimipramine with reduced CSF 5-hydroxyindoleacetic acid levels, but not plasma levels, of the drug [148]. Subsequently, chronic treatment with specific 5-HT reuptake inhibitors such as fluoxetine, zimeldine (Astra), sertraline (Pfizer) and fluvoxamine (Duphar) were also found to be effective anti-obsessional treatments [149,150] while the 5-HT releaser fenfluramine (Servier) can augment the therapeutic action of chlorimipramine [151]. Unfortunately, none of the treatments are effective in more than 50% of the patients and this is only reached after approximately 6 weeks treatment [145,149]. MAOIs, which acutely enhance extraneuronal 5-HT, are also clinically effective in OCD [145] although not in all studies [143]. But noradrenergic reuptake inhibitors are not effective[145].

The administration of mCPP orally to OCD patients provoked anxiety and this response was greater than in healthy volunteers [152]. The drug also exacerbated obsessive compulsive symptoms [96,152–154] which in some cases had been absent for several months, although this did not occur in the study of Charney *et al.* [155] in which intravenous administration was used. None of the studies reported the induction of panic attacks in OCD patients. The effect of mCPP on OCD symptoms was antagonised by metergoline [75,96] which is a non-specific 5-HT_1/5-HT_2 receptor antagonist [16]. Since mCPP and metergoline act as agonist and antagonist respectively at 5-HT_{1C} receptors, these findings may suggest that the receptors are in some way hypersensitive in OCD patients. Chronic administration of specific 5-HT reuptake inhibitors such as fluoxetine or MAOIs might therefore act by down-regulating these receptors, as suggested by evidence outlined in the section on depression and by the ability of chronic administration of fluoxetine and chlorimipramine to desensitise the behavioural effects of mCPP in OCD patients [157,158]. However not all evidence supports this hypothesis. Obsessive compulsive symptomology was not induced by MK 212 [156], an agonist at 5-HT_{1C} receptors [61] with roughly fifty-fold selectivity over 5-HT_2 receptors [16]. This may reflect the drug's poor selectivity over 5-HT_{1A} receptors [16] or its even higher affinity for the 5-HT_3 receptor (Table 3, [159]). Its affinity for many other sites is unknown and could also influence its effects on OCD patients, although in rats the stimulus cue of MK 212 generalized to mCPP and was blocked by metergoline and methysergide but not by specific 5-HT_2 receptor antagonists [160]. Another difficulty for the 5-HT_{1C} hypothesis of OCD is the failure of acute fenfluramine, the 5-HT releaser, to induce OCD symptomology in OCD patients [154,161]. Although this type of drug might be expected to stimulate many 5-HT receptor subtypes simultaneously, which could account for this finding, it too produces a stimulus in rats which generalizes to mCPP [160] and induces anxiety in rats by 5-HT_{1C} receptor stimulation [162]. It also has reasonable affinity for the 5-HT_{1C} receptor itself [163].

Evidence from neuroendocrine responses to mCPP is also inconsistent with 5-HT_{1C} receptor hypersensitivity in OCD. Patients had reduced cortisol responses to mCPP [152,156] and reduced prolactin responses in some [154,155,158] but not in all [152,154] studies. Responses of both hormones to MK 212 were also blunted [156]. Furthermore, although chronic fluoxetine [157] and chlorimipramine [158] abolished the ability of mCPP to increase obsessive and compulsive symptoms and anxiety, cortisol and prolactin responses were potentiated in the fluoxetine study [156], although increased plasma levels of mCPP could have been responsible [153]. Neuroendocrine evidence, therefore, suggests that 5-HT_{1C} receptors may be subsensitive in OCD in direct contrast to the behavioural data.

These apparent contradictions may be explained if the involvement of 5-HT_{1C} receptors in OCD symptomology resides in specific brain regions or if the hormonal responses to mCPP are not 5-HT_{1C} receptor mediated. The latter possibility seems unlikely, as clinically mCPP-

induced cortisol and prolactin secretion are blocked by metergoline [87,97] and the relatively selective 5-HT_2/5-HT_{1C} receptor antagonist ritanserin [83], although methysergide only blocked the prolactin response [97]. A third possibility is that a functional supersensitivity, which is either proximal or distal to the 5-HT_{1C} receptors, underlies OCD and that the receptors themselves are down regulated by compensatory mechanisms.

Table 4: Pharmacology of trifluoromethylphenylpiperazine (TFMPP), MK 212, Quipazine, 2,5-dimethoxy-4-iodoamphetamine (DOI) and (–)2,5-demethoxy-4-iodoamphetamine (–)(DOM); agonists at 5-HT_{1C} receptors

Receptor		5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_{1D}	5-$HT_{1D\alpha}$	5-$HT_{1D\beta}$	5-HT_{1E}	5-HT_2	5-HT_3
Drug	**Parameter**									
TFMPP	pK_D	6.5	6.9	7.3	6.6	7.1[g]	6.9[g]	5.2[b]	6.6[a]	
	pEC_{50}	6.7	6.9	6.8	5.8				6.1[b]	
	Efficacy	67.1	74.3	59.2	54.2				Ant[b]	
MK212	pK_D	5.3[c]	5.0[c]	6.2[c]	> 5.0 [f]			> 50[k]	4.8[c]	7.5[i]
	pDC_{50}			6.1[b]					4.7[b]	
	Efficacy			90[b]					80[b]	
Quipazine	pK_D	5.5	6.5	6.7	5.9				6.2	8.5
	pEC_{50}	5.2	6.2	6.2	5.7				5.0	
	Efficacy	Ant	Ant	63	Ant				80	Ant
DOI	pK_D	4.7[j]		7.8[d]	5.6 [j]			5.5 [b]	7.5[j]	
	pEC_{50}			7.0[d]						
	Efficacy			58[d]						
(-)DOM	pK_D			6.8[c]						
	pEC_{50}			6.1[c]						
	Efficacy			85[c]						

Values for pEC_{50} and efficacy (E_{max} as a percentage of that for 5-HT) for agonist activity, pK_B for antagonist efficacy and pK_D from receptor binding studies are given. The functional assay for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor was inhibition of forskolin-stimulated adenylate cyclase activity. The assay for 5-HT_{1C} and 5-HT_2 receptor function was stimulation of basal inositol phosphate accumulation in choroid plexus and cortical tissue, respectively. All data taken from [62] except:

[a] [16] [b] [61] [c] [424]
[d] [26] [e] [64] [f] G Price; personal communication
[g] [69] [h] [425] [i] [159] (pIC_{50}) [j] [432] [k] [AM Brown, Personal communication]

The effect of mCPP on OCD symptoms, unlike its actions in panic disorder (see above), is not typical of other anxiogenic drugs. Thus yohimbine [164], lactate [165] and caffeine [166] cannot induce or exacerbate obsessive compulsive symptomatology, suggesting the existence of a specific dysfunction. Interestingly, these symptoms are not induced in healthy volunteers. While the evidence points to this dysfunction possibly involving 5-HT_{1C} receptors, there is less evidence that an antagonist of these receptors would be of therapeutic benefit. Metergoline, the only 5-HT_{1C} receptor antagonist studied to date, was found to modestly reduce obsessive compulsive symptoms in one study [75] but not in a second [96]. The lack of effect of metergoline could reflect the drug's lack of speficity for 5-HT_{1C} receptors [16] (Table 1); indeed, in some clinical studies it was itself anxiogenic [132] and in one study it reversed the therapeutic action of chlorimpiramine, increasing anxiety and OCD symptomatology [167]. One possible property of metergoline that would be more prevalent in humans than in rodents is its agonist activity at 5-HT_{1D} receptors [168], the effects of which are, as yet, unknown. If 5-HT_{1D} receptor stimulation can induce OCD symptomatology, as has been suggested by Zohar & Kindler [169], this might underlie the action of mCPP which has agonist properties at 5-HT_{1D} receptors and relatively high affinity for the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ cloned human

receptors (Table 2). It might also be consistent with the failure of MK 212 to precipitate OCD symptomatology [156] as this drug has low affinity for the 5-HT$_{1D}$ receptor (Table 3), although its affinity for human 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors is unknown. However the effects of metergoline on OCD symptomatology are inconsistent (as outlined above) and yohimbine, another 5-HT$_{1D}$ partial agonist [168], had no effect [164].

Another possibility is that metergoline could be a 5-HT$_{1C}$ agonist at the human receptor. Alternatively the effects of 5-HT reuptake inhibitors and MAOIs could be caused by effects on sites other than the 5-HT$_{1C}$ receptor.

Drugs of abuse

Alcoholism

Alcoholism is estimated to have a lifetime occurrence of 11-16% of the American population [170], and 5-HT has long been thought to influence this condition. Low cerebral spinal fluid (CSF) levels of the principal metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), have been observed in alcoholics [171,172]. This would seem to be trait-dependent as they were also observed in abstinent alcoholics [171] or in those suffering from withdrawal symptoms after one week of abstinence [173]. Banki [174,175] reported a negative correlation between 5-HIAA levels and number of days of abstinence.

Animal studies have provided further evidence. Levels of 5-HT and 5-HIAA were found to be reduced in some brain regions of alcohol-preferring rats [176]. Acutely, alcohol increases 5-HT release [177] and metabolism [178,179] in the striatum and increases 5-HIAA levels in several other brain regions including the nucleus accumbens [176] while reduced 5-HT turnover has been observed after chronic treatment [180]. Low 5-HT function has therefore been proposed to promote alcohol consumption. Treatments which increase serotonergic function might thus be expected to reduce alcohol consumption, and this has indeed been reported. Administration of the 5-HT precursors tryptophan [181] or 5-hydroxytryptophan (5-HTP) [176], the 5-HT releasing agent fenfluramine [176] and the 5-HT reuptake inhibitors fluoxetine [182–184] and sertraline [185], all reduce alcohol consumption when given acutely to rats. Intra-nucleus accumbens 5-HT has a similar effect [186]. The 5-HT$_{1A}$ agonist 8-OH-DPAT [176,187,188], 5-HT$_2$ and 5-HT$_{1C}$ agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) (Table 3, [176]) and 5-HT$_{1B}$ and 5-HT$_{1C}$ agonist 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) (Table 3, [176]) also reduce consumption. Conversely, treatments that reduce 5-HT function, such as the 5-HT depletor para-chlorophenylalanine (PCPA) [189,190], enhance consumption. However the non-specific 5-HT$_1$ and 5-HT$_2$ receptor antagonists methysergide and metergoline [191,192] had no effect, while the 5-HT neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) had inconsistent effects [193,194].

Clinical trials are in agreement with results from animal models. In particular the 5-HT reuptake inhibitors fluoxetine, zimelidine, and citalopram (Lundbeck) all reduced the mean daily alcohol consumption of moderate alcoholics. The magnitude of this effect while consistently observed was only 9-17% [195–197]. Interestingly, the effect had a rapid onset, unlike the antidepressant actions of these drugs. This suggests mediation by increased synaptic cleft 5-HT levels. The 5-HT$_{1A}$ receptor agonist buspirone (Bristol-Myers Squibb) has also been shown to have modest clinical efficacy [198–200]. This could be mediated either by stimulation of postsynaptic 5-HT$_{1A}$ receptors, by desensitisation of cell body autoreceptors and hence enhanced 5-HT release [201], or acutely by stimulating these autoreceptors and hence decreasing 5-HT release.

In view of the above evidence that enhanced 5-HT suppresses ethanol intake, the effects of mCPP on alcoholics are surprising. The drug was reported to induce an alcohol-like 'high' feeling in alcohol abstaining alcoholics and, in a third of the subjects, induced a craving to drink alcohol [202]. One explanation for these results, proposed by Sellers *et al.* [203], is that mCPP can induce an ethanol-like stimulus. This is supported by the reported similarity between the ethanol cue in a rat drug discrimination paradigm and that of TFMPP [204], a 5-HT_{1C}/5-HT_{1B} agonist resembling mCPP both pharmacologically (Table 3) and behaviourally in rats [59,60,88,205]. The perception of an alcohol-like stimulus in the absence of the full pharmacological effect may therefore cause craving.

An alternative explanation is that alcoholism is related to obsessive compulsive disorder [206]. Like alcoholism, OCD can be characterised by low 5-HT function [144,147], is ameliorated by specific 5-HT reuptake inhibitors (albeit after chronic administration [149]) and can be precipitated by mCPP (see above). It has also been suggested that the craving response to mCPP is secondary to the induction of anxiety [203], since alcoholism often coexists with anxiety [207]. This seems the least likely explanation, as anxiety induction was not noted in the Benkelfat *et al.* [202] study. However, the clinical efficacy of buspirone might be secondary to anxiolysis [208].

The pharmacology of mCPP (Table 2) suggests that 5-HT_{1C} receptors may account for these actions. Recent reports that the 5-HT_{1C} and 5-HT_2 antagonist (Table 1) ritanserin can reduce alcohol preference in rats [209] are possibly consistent with this. The effect was accompanied by increased water intake. It was not mediated by alcohol aversion nor by altered alcohol metabolism, and was not associated with body weight changes [209]. It may therefore specifically affect addictive mechanisms. Although this study reported effects at low doses, which might not be expected to block 5-HT_{1C} receptors *in vivo* [66], only high 5-HT_{1C} receptor blocking doses [66] were effective in a second model [210]. Ritanserin was also found to markedly reduce the alcohol intake of a small group of chronic alcoholics [211]. These patients reported that they had little difficulty in containing their consumption even after two weeks withdrawal from the drug. Mediation of these effects by 5-HT_2 receptor blockade seems unlikely: firstly mCPP is a 5-HT_2 receptor antagonist (Table 2), and secondly the specific 5-HT_2 receptor antagonist ketanserin (0.4 mg/kg *po* one hour pretest) did not affect rat alcohol preference in a recent study [210]. The reported ability of DOI and TFMPP, agonists at 5-HT_{1C} receptors, to reduce alcohol consumption in rat models [176] may be due to their anorexic [205,212], sedative [59,213] or, in the case of DOI, hallucinogenic [214] actions. These effects were not reported in the clinical study of Benkelfat *et al.* [202]. The predominance of the craving response to mCPP in alcoholics may suggest hypersensitive 'craving' mechanisms.

In conclusion, the opposing effects of mCPP and ritanserin, both clinically and in animal models, must be considered evidence of possible 5-HT_{1C} involvement. Further evidence must await the development and testing of more selective compounds. Indeed the effects of mCPP and ritanserin, while seemingly behaviourally specific and opposite, may be unrelated, as may be the case if ritanserin were acting as an anxiolytic (see above). The opposite nature of the effects of treatment which enhance 5-HT function such as 5-HT reuptake mechanisms (see above) and the mCPP/ritanserin studies, suggest the existence of several serotonergic mechanisms modulating alcoholism. When 5-HT function is enhanced at several receptor subtypes simultaneously the net result is alcohol intake inhibition. Conceivably this also occurs when 5-HT_{1C} receptors are selectively blocked. Given the modest clinical efficacy of 5-HT reuptake inhibitors there is considerable scope for new forms of treatment.

Other drugs of abuse

In addition to its effects on alcohol abuse, ritanserin has been anecdotally noted to be of use in patients withdrawing from other drugs of abuse [214]. This has led to an examination of its actions in rat models of cocaine and opiate dependence. Ritanserin was found to reduce both cocaine and fentanyl (Janssen) preference of rats [216,217]. The magnitude of the effect on cocaine was less than that observed for alcohol but greater than that observed with fentanyl [217]. This probably reflects the degree of reinforcement engendered by the drugs. Ritanserin does not interact with the cues for cocaine or fentanyl [216,217] which argues against any direct effects of the drug. Since drugs of abuse are thought to induce reinforcing effects by activating the dopamine reward pathways of the nucleus accumbens [218], it is of interest that ritanserin does not affect intracranial self-stimulation [216,217] which is thought to act on the same system. Ritanserin may therefore have a specific action on a reinforcing pathway common to drugs of abuse and perhaps distal to dopaminergic mechanisms of the nucleus accumbens. Whether this is 5-HT$_{1C}$ or 5-HT$_2$ receptor mediated is not yet clear.

Depression

A large body of evidence suggests that the serotonergic system is defective in depression. Most neurochemical and neuroendocrine studies of depressive patients are consistent with the existence of a serotonergic deficit, while SSRIs and MAOIs are clinically effective antidepressants and both increase extraneuronal 5-HT acutely (for review, see [219]).

One argument in favour of 5-HT$_{1C}$ receptor involvement in depression is the clinical efficacy of three 5-HT$_2$/5-HT$_{1C}$ receptor antagonists: mianserin [125,126,128], cyproheptadine [220] and ritanserin [221-223]. However, none of these drugs has been reported to exert immediate therapeutic action [221,223]. This may argue against simple 5-HT$_{1C}$ receptor blockade as a mode of action. Alternatively it might reflect a property of the disease state.

Clinically, the effect of treatments expected to enhance 5-HT$_{1C}$ function is also unclear. Thus mCPP administration to healthy volunteers did not cause depressive symptoms in most studies [80,81,84,134,224-226], with one exception [86]. In addition it does not potentiate depression in depressive patients and neither cortisol nor prolactin responses in these patients differed from that of healthy volunteers [133,134,226]. Indeed when given subchronically it ameliorated depressive symptomatology in elderly depressives [227]. These findings argue against direct 5-HT$_{1C}$ involvement in depression. However antidepressants may exert their therapeutic efficacy after chronic administration through adaptive changes to the serotonergic system [228], and, in particular, to the 5-HT$_{1C}$ receptor, as suggested by studies in rats. These involve models of 5-HT$_{1C}$ receptor function and are summarised in Table 5. Chronic treatments with the MAOIs phenelzine (Parke-Davis) or nialamide (Pfizer) have been reported to desensitise mCPP-induced hypolocomotion [229], a putative 5-HT$_{1C}$ mediated behaviour (Table 3, [59]). The MAOI tranylcypromine (SmithKline Beecham) reduced mCPP-induced penile erections [230], another putative 5-HT$_{1C}$ mediated response (Table 3, [231]) after chronic treatment, while chronic clorgyline reduced mCPP-induced hypophagia [232] and hyperthermia [233]. Of these last two paradigms mCPP-induced hypophagia is relatively well characterised as 5-HT$_{1C}$ mediated (Table 3, [59,66]) while hyperthermia is likely to be 5-HT$_{1C}$ mediated (Table 3, [233]). The effects of selective 5-HT reuptake inhibitors have been less extensively studied. One such drug, chlorimipramine [181] reduced mCPP-induced hypothermia after chronic treatment [233] while both chronic sertraline and citalopram reduced mCPP induced hypolocomotion [234]. However, chronic ORG 6997 (Organon) did not affect the rat penile erection model [230]. Noradrenergic reuptake inhibitors do not appear to share these properties. Thus, although imipramine (Ciba-Geigy) [181] reduced hyperthermic

responses to mCPP [233], it potentiated mCPP-induced hypolocomotion [235] and prolactin release but did not affect corticosterone or growth hormone release [236]. Also another noradrenergic reuptake inhibitor, desipramine (Ciba-Geigy) [181], did not alter the hypolocomotor response [229]. The atypical antidepressant iprindole (Wyeth Research) was also without effect after chronic administration [229]. These findings might be caused by altered metabolism or disposition of mCPP, but they suggest that, in rats, treatments that enhance extraneuronal 5-HT levels desensitise 5-HT_{1C} receptor function. This in turn may cause, or contribute to, their antidepressant efficacy. The therapeutic effect of subchronic mCPP [227] could therefore also be explained by 5-HT_{1C} receptor desensitization. Indeed, chronic mCPP desensitises mCPP-induced hypolocomotion [237-239] and changes in cerebral glucose metabolism [238] without altering its pharmacokinetic profile [238,239]. Chronic imipramine treatment is reported to reduce the hyperthermic effects of mCPP in humans [157] and in rats [233].

Table 5: The effects of chronic antidepressant treatments on putative rat models of 5-HT_{1C} receptor functional activity.

Treatment		Paradigm (mCPP-induced)	Effect	Reference
Class	**Drug**			
MAOI	Phenelzine	Hypolocomotion	Decrease	229
	Nialamide	Hypolocomotion	Decrease	229
	Tranylcypromine	Penile erections	Decrease	230
	Chlorgyline	Hypophagia	Decrease	232
		Hyperthermia	Decrease	233
SSRI	Chlorimipramine	Hyperthermia	Decrease	233
	Sertraline	Hypolocomotion	Decrease	234
	Citalopram	Hypolocomotion	Decrease	234
	ORG 6997	Penile erections	-	230
SNRI	Imipramine	Hyperthermia	Decrease	233
	Desipramine	Hypolocomotion	Increase	235
		Hypolocomotion		229
Atypical	Iprindole	Hypolocomotion		229

MAOI: monoamine oxidase inhibitor
SNRI: selective noradrenergic reuptake inhibitor
SSRI: selective serotonin (5-HT) reuptake inhibitor
Atypical: atypical antidepressant

This may suggest that 5-HT_{1C} receptors can be desensitised by this drug or that body temperature is affected by some other mechanism. Whether all these results can be safely interpreted as evidence of 5-HT_{1C} receptor desensitization awaits studies of 5-HT_{1C} receptor binding and PI hydrolysis.

Finally, the specific 5-HT reuptake inhibitor fluoxetine (a racemic mixture) and its (-) isomer have been shown to have some affinity for the 5-HT_{1C} site [240]. Since this is roughly ten-fold less than their affinities for the 5-HT reuptake site it may not explain their antidepressant efficacy. Fluoxetine is metabolised to the long-acting metabolite norfluoxetine. This too has

been found to bind to 5-HT_{1C} receptors, and a patent for its use in feeding disorders, OCD, alcoholism, sleep disorders and migraine has been published [502].

In conclusion, the evidence for a role for 5-HT_{1C} receptors in depressive illness is at present neither wholly consistent nor complete. The therapeutic benefit of ritanserin (and presumably mianserin and cyproheptadine) may be secondary to improved sleep, anti-anxiety and energy restoring properties. Some of these at least may not be 5-HT_{1C} mediated.

Migraine

When mCPP was administered to bulimic patients, migraine-like headaches were reported eight to twelve hours later [241]. This response was correlated with plasma levels of mCPP and was more pronounced in patients with a personal or family history of migraine, an effect confirmed in a recent study of migraine patients [242]. Migraine patients given mCPP had enhanced cortisol and temperature responses [242]. Fozard & Gray [243] have argued that 5-HT_{1C} receptor stimulation might be an important step in the pathogenesis of migraine for two reasons: firstly, mCPP activates 5-HT_{1C} but antagonizes 5-HT_2 receptors (see mCPP section). and secondly, methysergide pizotifen, mianserin and cyproheptadine, all of which are non-specific 5-HT_{1C} and 5-HT_2 receptor antagonists are clinically effective antimigraine agents, but the selective 5-HT_2 antagonist [16] ketanserin is not [244]. Recently Brown *et al.* [63] have demonstrated that two effective antimigraine agents, ergotamine (Wellcome) and dihydroergotamine (Sandoz), are also potent 5-HT_{1C} agonists but only occasionally induce headaches [245]. However, this may be due to the additional potent 5-HT_1-like constrictor activity of these drugs on large dilated cerebral arteries [63], which may confer antimigraine efficacy [245], this action is shared by sumatriptan (Glaxo), a novel antimigraine agent [246]. Since both drugs also activate other receptors (e.g. α adrenoceptors and dopamine receptors) these could conceivably mediate their effects [247]. It could also be argued that the α_1 adrenoceptor blocking activity of ketanserin (Table 1) prevented antimigraine efficacy. The relationship of 5-HT_{1C} receptors to the clinical efficacy of the 5-HT_{1C}/5-HT_2 receptor antagonists may also be disputed since they too have additional actions. Thus cyproheptadine and pizotifen have similar and appreciable affinities for dopamine, muscarinic cholinergic and α_1 adrenoceptor sites, and lower affinities for α_2 adrenoceptors (Table 1). They also have an affinity for histamine H_1 receptors equal to that for 5-HT_2 and 5-HT_{1C} sites (Table 1, [15]). Mianserin, too, has affinity for histamine H_1 receptors and lower affinity for both α_1 and α_2 adrenoceptors, but has low affinity for dopamine receptors and is inactive at cholinergic receptors (Table 1, [15]). Methysergide, however, has little affinity for histamine, α adrenoceptors or cholinergic receptors (Table 1, [15]). These four drugs, therefore, only share high affinity at the 5-HT_2 and 5-HT_{1C} sites, and the lack of clinical efficacy of histamine H_1, cholinergic, dopaminergic or α adrenoceptor antagonists [248] suggests that 5-HT_{1C}/5-HT_2 receptors alone are clinically relevant. The modest antimigraine efficacy of ICI 169,369 [249], another relatively specific 5-HT_2 and 5-HT_{1C} receptor antagonist [100,250], may be attributable to the dose used, while the clinical efficacy of chronic administration of 5-HT reuptake inhibitors such as amitriptyline (Merck Sharp & Dohme) [251] and fluoxetine [252,253] as migraine prophylactics may be caused by down-regulation of 5-HT_{1C} receptors (see section on depression and Table 5).

One interesting observation of the migraine-precipitant action of mCPP is the long time interval between administration and headache; peak mCPP concentrations were seen two to three hours after administration [241,242], whereas headache occurred up to twelve hours later.

This suggests an indirect mode of action and may be consistent with the prophylactic but not acute efficacy of 5-HT_{1C}/5-HT_2 receptor antagonists in migraine [243].

In conclusion, 5-HT_{1C} receptors may be involved in migraine. Further proof awaits the development of more specific compounds and further testing of existing drugs.

Sleep Disorders

In man, the serotonergic system has been considered hypnogenic. Treatments that enhance 5-HT function, such as the administration of the 5-HT precursors tryptophan [254,255,256] or 5-hydroxytryptophan (5-HTP) [256,257], increase either sleep time, the duration of slow wave sleep (SWS) or the duration of rapid eye movement sleep (REMS). Conversely the 5-HT depleter PCPA reduces REMS [258]. In cats, PCPA or 5-HT neurotoxic lesions can lead to total insomnia that can be reversed by 5-HTP [256]. As with many other functions of 5-HT, the recognition of 5-HT receptor subtypes has suggested that 5-HT may have differing effects on sleep depending on which subtype is studied. 5-HT_{1A} receptor agonists, for instance, increase wakefulness in both rats [259,260] and humans [261].

MCPP reduced total sleep time, sleep efficiency, SWS and REMS in two clinical studies [262,263]. Wakefulness was increased and subjective behavioural effects of mCPP seemed more prominent than in patients given mCPP during waking hours [262]. This may reflect the absence of environmental distraction. The effects of mCPP are consistent with reports that the 5-HT reuptake inhibitors zimelidine and indalpine (Groupe Pharmuka) also reduce total sleep time and REMS when given acutely [264]. In rats the mixed 5-HT_2/5-HT_{1C} agonist 2,5-dimethoxy-4-methylamphetamine (DOM) (Table 3) reduced both SWS and REMS [265]. The effects of the 5-HT reuptake inhibitor zimeldine are more complex. Initially it is reported to increase wakefulness and reduce REMS but after roughly two hours it enhances SWS [266]. Other 5-HT reuptake inhibitors, such as fluoxetine [267], indalpine [268] and alaproclate (Astra) [269], also reduce REMS and can enhance SWS [267,270]. The biphasic effects of this class of compounds is likely to reflect the stimulation of different 5-HT receptor subtypes by the released 5-HT. The increased wakefulness is unlikely to be 5-HT_2 or 5-HT_{1C} receptor mediated as it is not blocked by ritanserin [266]. Curiously, TFMPP given to rats reduced REMS but also increased SWS in the second hour after administration, although this effect was not dose-dependent [267]. The drug's profile of action was thus dissimilar to that of mCPP in humans but similar to 5-HT reuptake inhibitor; its action may therefore be due to 5-HT releasing properties [71].

The effect of drugs with 5-HT_{1C} antagonist properties is clearer. The 5-HT_2 and 5-HT_{1C} receptor antagonist, ritanserin, increases SWS, reduces sleep onset latency and improves subjective sleep quality in both young [272-274] and old [275] healthy volunteers. REMS is reduced in some [272,276] but not all [275,277] reports. A shift from early stage SWS to later, deeper SWS stages is generally reported [272,273,275-277]. Ritanserin has also proved efficacious in insomniac patients [278] and patients suffering from dysthymia (depressive neurosis) [277]. The drug achieved these effects acutely [273,275,276,279], chronically [273,275,277] and dose-dependently [276]. Only Adam & Oswald [275] reported withdrawal wakefulness. Other drugs with 5-HT_{1C} antagonist actions such as mianserin [280], cyproheptadine [281,282] and pizotifen [283] have similar effects, but methysergide [284] and metergoline [282] do not. This may reflect the lack of specificity of these compounds (Table 1, [16]) such as their 5-HT_{1D} partial agonist actions [168]. In rats, too, ritanserin increases SWS [265,266,285] although not always significantly [18]. However, some studies suggest that the deepest phase of SWS (SWS2) is increased but total SWS is not [266,285] and not all report

significantly reduced wakefulness [18,266]. As in clinical studies, REMS was reduced [18,265,285] although not universely [266]. Only one study of the effects of two other 5-HT_2/5-HT_{1C} receptor antagonists with an otherwise relatively clean profile of action, ICI 169,369 [250] and ICI 170,809 (Table 1), has been published. However while they increased REMS latency, as did ritanserin, ICI 169,369 had no effect and ICI 170,809 had little effect on SWS, although in the same study ritanserin reduced it [286]. Unfortunately SWS in this study was not subdivided into SWS1 and SWS2. Thus both antagonists might have increased SWS2 as seen by others. The effect of ritanserin on all sleep stages can be reversed by the 5-HT_{1C}/5-HT_2 agonist DOM [287]. Recently the effect on rat sleep patterns of SR 46349B, a relatively selective 5-HT_2 receptor antagonist (Table 1) was studied. This drug also reduced REMS and increased REMS latency, as did ritanserin [18]. This suggests that 5-HT_2 receptor antagonism mediates this effect. As neither SR 46349B nor ritanserin clearly affected SWS or wakefulness in this study it is not possible to decide whether these functions are 5-HT_2 or 5-HT_{1C} receptor mediated [18].

The shift in sleep pattern derived from ritanserin and other 5-HT_2/5-HT_{1C} receptor antagonists is subjectively reported to be beneficial and refreshing despite the reduced amount of REM sleep. The effects are also not associated with sedation [272]. Given the largely opposite effects of mCPP it seems possible that 5-HT_{1C} receptors might mediate these actions. Should reduced REMS be caused by 5-HT_2 receptor blockade, as suggested by the results of Rinaldo-Carmona *et al.* [18], and should increased SWS and reduced wakefulness be 5-HT_{1C} receptor mediated, then selective 5-HT_{1C} antagonists could be of particular therapeutic use in the treatment of sleep disorders. Further trials with more selective drugs are awaited.

Feeding Disorders

Administration of mCPP and TFMPP to food-deprived [60,428,430] or freely feeding [205] rats reduces subsequent food, but in the case of mCPP, not water [288] intake. The effect is not secondary to anxiety as it is not reversed by benzodiazepine anxiolytics [88]. Nor is it likely to be secondary to hypolocomotion as, unlike hypophagia, the effect is not blocked by either cyanopindolol or (–)propranolol [60]. Also TFMPP administration into the hypothalamus causes hypophagia only [289]. Since the hypophagia was not blocked by the antiemetic trimethobenzamide, mCPP is unlikely to induce nausea [290]. The accelerated appearance of the postprandial satiety sequence following both mCPP and TFMPP suggests that a satiety mechanism is probably responsible for their hypophagic actions [Kitchener & Dourish, unpublished observations].

The action of mCPP was blocked by the non-selective 5-HT_2/5-HT_{1C} receptor blockers metergoline, mianserin, mesulergine and 1-NP but not by the selective 5-HT_2 antagonist ketanserin or 5-HT_3 antagonist ICS 205,930 (Table 4, [60]). Inhibition of mCPP-induced hypophagia by ten antagonists was found to correlate only with their affinities for the 5-HT_{1C} site [66]. Studies on the pharmacology of TFMPP-induced hypophagia have produced a less clear discrimination between the effects of 5-HT_{1C} and selective 5-HT_1 receptor antagonists (Table 3, [430]). MK 212 also reduces feeding in rats [291] but the mechanism of action is unknown. The hypophagic effects of DOI [292] and quipazine (Miles Scientific) [293], both of which have high affinity for the 5-HT_{1C} site [16,26], have been reported to be mediated by 5-HT_2 receptors because they are ketanserin sensitive.

This may reflect differences in experimental design but is most likely to be secondary to response competition between feeding and the behavioural effects of 5-HT_2 receptor

stimulation, one possibility being hallucination [214]. Indeed DOI, at least, disrupts the postprandial satiety sequence [294] while quipazine reduces water intake also [288].

The effects of 5-HT_1/5-HT_{1C} antagonists have also implicated 5-HT_{1C} receptors in the control of food intake. Mianserin, cyproheptadine and 1-NP all increased the food intake of freely feeding rats over four hours as did mesulergine, albeit not significantly [60]. Likewise Dourish *et al.* [295] observed increased food intake after administration of metergoline, methysergide, mianserin and methiothepin. Metergoline, ritanserin and methysergide increased the consumption of palatable wet mash in rats partially sated prior to drug injection [296]. In contrast, the specific 5-HT_2 antagonist ketanserin had no effect on food intake in freely feeding rats [59,295]; neither did ritanserin at low doses [295,297] which may not block 5-HT_{1C} receptors [66]. Increased food intake is only seen under conditions of satiety where low rates of feeding occur. Under conditions of high feeding rates none of these drugs was effective [60,296]. This is consistent with mediation by blockade of satiety signals and may explain the contradictory findings of cyproheptadine's hyperphagic actions [298,299]. It is also of interest that the hyperphagic effects of these compounds has only rarely been observed to increase daily food intake or body weight [60,295,300-302], the exceptions being metergoline [295] and high doses of ritanserin [297]. This may suggest the presence of compensatory mechanisms.

In healthy volunteers or bulimics, mCPP has not been reported to affect appetite [303] possibly due to the short nature of most studies which are not designed to elicit changes in appetite. Since mCPP-induced anxiety is seen at doses ten-fold less than those necessary for hypophagia in rats [60,205], the doses used clinically may have been too low. However fenfluramine, a drug that enhances synaptic cleft 5-HT, is a noted, clinically effective anorexic agent [304]. It has been claimed to act via 5-HT_2 receptors in rats as it was blocked by ketanserin [305], but this was not confirmed by Neil & Cooper [288]. This group concluded that fenfluramine anorexia was 5-HT_1, but not 5-HT_{1A} or 5-HT_{1B}, mediated. However they could not block the effects of fenfluramine with the non-specific 5-HT_2/5-HT_{1C} receptor antagonist ICI 169,369 (Table 1, [17,100,250]) and only achieved a modest non-significant antagonism with mianserin. Consistent with these results were those of Garattini *et al.* [306], which showed antagonism of fenfluramine by metergoline but not by doses of ritanserin that might be specific for 5-HT_2 receptors [66]. However, a firm attribution of fenfluramine's actions (or at least a component of them) to 5-HT_{1C} receptor stimulation is not possible at present, although the drug has considerable affinity for the 5-HT_{1C} receptor [163] and has been reported to cause anorexia in rats pretreated with the 5-HT synthesis inhibitor p-chlorophenylalanine [307]. This suggests that the drug may act directly on postsynaptic 5-HT_{1C} receptors.

A second class of drugs that increase synaptic cleft 5-HT, the specific 5-HT reuptake inhibitors, are also clinically effective anorexic agents [308,309]. Fluoxetine [310-312], paroxetine (SmithKline Beecham) [309], zimelidine (Astra) [313], RU 25591 (Roussel UCLAF) [314] and sertraline [315,316] are hypophagic in rodents. Like fenfluramine the mode of action of these drugs is uncertain. Although the effect of sertraline was blocked by metergoline and methysergide, but not ketanserin [315], fluoxetine was not blocked by metergoline or LY 53857 [317], both of which are non-specific antagonists of 5-HT_{1C} receptors (Table 1). The effect of drugs which enhance extraneuronal 5-HT may be mediated via more than one 5-HT receptor subtype. Thus 5-HT can reduce food intake when injected into the paraventricular nucleus of the hypothalamus [318] or when given peripherally [319]. Both 5-HT_{1B} and 5-HT_{1C} receptors may mediate central hypophagic mechanisms [60,289], while 5-HT_2 receptors may mediate them peripherally [297,319,320]. The above evidence shows that the hypophagic actions of treatments which may enhance 5-HT_{1C} receptor function

are not well characterised in species other than rodents. Clinically effective anorectic agents may therefore attain their efficacy via mechanisms other than 5-HT_{1C} receptor stimulation.

Obesity

The hypophagic effects of 5-HT_{1C} receptor stimulation might be applied as an aid to weight loss, particularly where obesity is life threatening, as in those with cardiovascular disease. The 5-HT reuptake inhibitor fluoxetine has been shown to induce weight loss in obese patients [321-323] albeit not of great magnitude. Fenfluramine has long been recognised as an effective anorexic agent [304]. This drug achieves its anorexic response rapidly to give a new body weight set point which is often lost on withdrawal. Since the drug can induce 5-HT lesions [304], albeit at high doses, alternative therapies might well be more acceptable.

Bulimia Nervosa

Another possible indication is Bulimia Nervosa. This disorder is estimated to affect 1.3-10.1% of American women [79] and is characterised by compulsive eating binges followed by self-induced vomiting, laxative abuse, or other methods to prevent weight gain. It can cause serious morbidity and even mortality. Fenfluramine has been claimed to have beneficial effects in bulimics, reducing bingeing [324] in one acute study. A second study observed reduced bingeing within a week of chronic fenfluramine administration [325]. In both studies fenfluramine may have acted by a direct reduction of feeding behaviour, as Blouin *et al.* [325] reported a reduction in caloric intake in the fenfluramine treated patients. Antidepressants represent a second class of treatment. Thus monoamine oxidase inhibitors such as phenelzine [326] and isocarboxazid (Roche) [327], which would be expected to increase extraneuronal 5-HT levels, are clinically effective. The specific 5-HT reuptake inhibitor fluoxetine is also effective [79,328]. Interestingly so is trazodone [329], which could act via its metabolism to mCPP [56]. The onset of fluoxetine's therapeutic effects is rapid [79] suggesting that, as with fenfluramine, appetite suppression may be involved. This is consistent with the reported relapse of two fluoxetine treated patients when given the 5-HT_{1C}/5-HT_2 receptor antagonist cyproheptadine [330]. However the noradrenergic reuptake inhibitors [146] imipramine [331], desipramine [332] and nomifensine (Hoechst) [333] are also effective, which could reflect the considerable overlap between depression and bulimia [328]. One antidepressant that was not effective in the treatment of bulimia was mianserin [334]. Since blockade of 5-HT_{1C} receptors by this drug [16] may enhance appetite (see above and the following section) this may not be surprising. However, chronic administration of antidepressants that enhance extraneuronal 5-HT may down-regulate 5-HT_{1C} receptors (see section on depression and Table 5), which could detract from efficacy. The possibility remains that 5-HT_{1C} receptor agonists might be of use in the treatment of Bulimia Nervosa.

Anorexia Nervosa

Clinically the non-specific 5-HT_{1C}/5-HT_2 antagonists cyproheptadine [301,302,335,336] and pizotifen [337,338] stimulate appetite. Both of these drugs also share a high affinity for histamine receptors (Table 1, [15]). However mianserin, methysergide and metergoline are not reported to increase weight [306,339]. These discrepancies might result from the non-specific nature of the drugs. The effect of the relatively specific 5-HT_{1C}/5-HT_2 receptor antagonist ritanserin might therefore be more relevant. Out of six large clinical trials with this drug, only one reported mild weight gain as a side effect [223] and this was tolerated after the first month. Another study [131] observed one case of increased appetite in twenty-two patients given 5 mg/kg daily for four weeks but other groups using higher [130,141,221] or similar doses [129] did not. No effects on appetite were reported in several smaller trials [272,275,279].

Furthermore, no alterations in appetite were observed in a study with ICI 169,369 on migraine [249]. One reason for the discrepancy between the effects of cyproheptadine and pizotifen and the studies of ritanserin may be that the latter were not set up to study appetite, which might thus have been overlooked. Alternatively the expected increase in appetite may be mild in most patients.

The above properties suggest that 5-HT_{1C} receptor antagonists might be of use in the treatment of anorexia nervosa. However, to date, no drug has consistently proved effective in this disorder. If appetite stimulation could improve the symptomology of anorexia one would predict that 5-HT_{1C} receptor antagonists or chronic treatment with antidepressants which enhance extraneural 5-HT might prove effective. Since neither the 5-HT_{1C}/5-HT_2 receptor antagonist cyproheptadine [340,341,342] nor the 5-HT reuptake blocker chlorimipramine [343] had therapeutic value in anorexics, this seems unlikely.

5-HT_{1C} receptors and feeding disorders: Summary

In conclusion 5-HT_{1C} receptor stimulation is very likely to mediate hypophagia. This might suggest therapeutic utility in obesity and in the control of binge eating in bulimics. Unfortunately the anxiogenic properties of 5-HT_{1C} receptor agonists might prove a significant contraindication in the absence of any evidence that 5-HT_{1C} receptor subtypes exist that differentiate between the two actions. The possibility of tolerance to repeated administration of 5-HT_{1C} receptor agonists, as reported by Sills *et al.* [237], Freo *et al.* [238] and Ulrichsen *et al.* [239], might also be a problem. 5-HT_{1C} receptor blockade may produce increased appetite and weight gain. Drugs with these properties could therefore prove useful in the treatment of anorexia nervosa.

Cognition impairment

Although data on the role of 5-HT in learning and memory has been inconsistent, it is generally thought treatments that enhance 5-HT function led to impaired learning and memory [344]. It was therefore surprising when animal studies with 5-HT reuptake inhibitors such as alaproclate, zimeldine [345] and fluoxetine [346,347] observed cognitive enhancement after acute administration. Altman *et al.* [348], however, reported that the effects of alaproclate and zimeldine were opposed by pretreatment with quipazine, a 5-HT agonist, but not affected by cyproheptadine. They speculated that the effects of 5-HT reuptake inhibitors may be mediated by effects other than enhanced extraneuronal 5-HT [348].

Clinically, a number of studies have reported cognition-enhancing effects of reuptake inhibitors. Thus chronic citalopram (Lundbeck) improved concentration and absent-mindedness in demented patients [349] but this effect was not reproduced in a second larger study [350]. Chronic fluoxetine enhanced memory function in depressive patients in two studies [351,352] but not in a third [353]. However, as depression impairs cognition [351], these effects may be secondary to clinical improvement. Chronic zimeldine attenuated alcohol-induced memory impairment [354] and chronic fluvoxamine was reported to improve memory task performance in patients with alcohol amnesic disorder [355]. In healthy volunteers neither acute [356,357] nor subchronic fluvoxamine had any effect on learning and memory performance [358]. Chronic clomipramine enhanced verbal fluency, the ability to recognise nonsense words and motor function [359], while acute sertraline was considered to induce an 'alerting' response [360]. However in elderly volunteers subchronic fluvoxamine had little effect on psychomotor function [361] as did subchronic treatment with sertraline which, in addition, had no effect in memory tests [362]. The studies seem to suggest that clinically, chronic treatment with this class of drugs is more likely to produce enhanced cognition. This

may therefore be caused by the induction of neurochemical changes such as receptor down-regulation (see section on depression).

MCPP has been administered to Alzheimer's disease patients and produced an elevated anxiety response compared with normal age-matched volunteers at a higher [225] but not at a lower [224] dose. Cognition was also impaired to a greater extent at the higher dose [225] but only the lower dose of mCPP was found to worsen episodic memory of the elderly volunteers [224]. These effects could well be secondary to anxiety or light-headedness/dizziness [84,224,225]. MCPP-induced cortisol and prolactin release was not altered in Alzheimer patients after either low [224] or higher [225] doses.

Drugs with 5-HT_{1C} receptor antagonist properties have been reported to enhance cognitive performance in some animal studies. Thus post-training mianserin, metergoline and methysergide improved memory of mice for an aversive behaviour [363]. Mianserin also attenuated age-induced deficits in passive avoidance retention of rats [264] and protected rats against an hypoxia-induced deficit [347]. These effects are probably 5-HT_2 mediated, as the selective 5-HT_2 receptor antagonist ketanserin [16] had similar effects in all three models [363,364,367].

Clinically, chronic mianserin tended to impair the performance of both psychomotor and memory tests [358,361,362]. This effect was thought to be secondary to the drug's sedative properties and was less pronounced after several days of treatment. Sedative properties are common to most of the older 5-HT_{1C}/5-HT_2 receptor antagonists due to their affinity for histamine H_1 receptors (Table 1) and was thought to account for the psychomotor retarding effects of acute cyproheptadine, although memory was unaffected in this study [365]. One other such drug, ritanserin, has been reported to enhance motivation and increase subjective energy levels [221]. At present, therefore, there is little evidence to support a role for 5-HT_{1C} receptors in cognition.

Schizophrenia

MCPP has been reported to increase [366-368], have no effect [369], or decrease [370] psychotic symptomology. Blunted ACTH and prolactin responses to mCPP have been reported by Iqbal *et al.* [368] but were not seen in other studies [366,369,370], although Kahn *et al.* [370] reported blunted temperature responses to mCPP. Negative symptoms were unaltered by mCPP [366].

Conversely ritanserin has been reported to reduce negative/affective symptoms in schizophrenia (anergia, anxiety/depression, activity, hostility [221,371,372]), as has cyproheptadine [373]. Ritanserin is also reported to reduce neuroleptic-induced extrapyramidal side effects [374] and those induced by the dopamine precursor DOPA in patients with Parkinson's disease [375,376]. Furthermore it may prevent neuroleptic-induced akathesia [377]. These properties are shared by the atypical antipsychotic clozapine, on which basis it is considered to be superior to classical neuroleptic agents [378]. Since, like ritanserin, clozapine has high affinity for 5-HT_2 receptors (Table 6, [378]) and an even higher affinity for 5-HT_{1C} sites (Table 6, [379]), these might mediate their actions. Indeed a high affinity for the 5-HT_{1C} receptor is also possessed by several other putative atypical [380] antipsychotic agents including tiospirone (Mead Johnston) [379,380], fluperlapine (Sandoz) [380] and rilapine (Knoll Pharmaceuticals) [380]. However similar efficacy against negative symptoms and neuroleptic-induced extrapyramidal side effects has also been claimed for setoperone [381], risperidone [372] and melperone (Pharmacia) [382-384] while preclinical evidence suggests

that amperozide (Pharmacia) [385-387] is also atypical. All of these drugs have moderate or, in the case of amperozide and melperone, submicromolar affinities for the 5-HT_{1C} site [16,379,380]. Clearly no correlation can exist between 5-HT_{1C} receptor affinity and atypical antipsychotic properties. However, all the above compounds also have considerable affinity for the 5-HT_2 receptor [16,379,380] with tiosperone, rilapine, risperidone, setoperone, amperozide and melperone having between twenty- and one hundred and sixty-fold selectivity for the site [16,379,380], although tiosperone was not selective in the study of Canton *et al.* [379]. Hence 5-HT_2 receptor antagonism is much more likely to be the determinant of an atypical antipsychotic profile, although this does not account for the absence of such properties from chlorpromazine, spiperone and loxapine – all of which have high affinity for both 5-HT_2 and dopamine D_2 sites [380]. As 5-HT_{1C} receptors do not seem to be important in the action of antipsychotic drugs the induction of psychotic symptoms by mCPP is either secondary to anxiogenesis or mediated by properties unrelated to 5-HT_{1C} receptors. Such an effect may be observed by the drugs antagonist efficacy at 5-HT_2 receptors (Table 2).

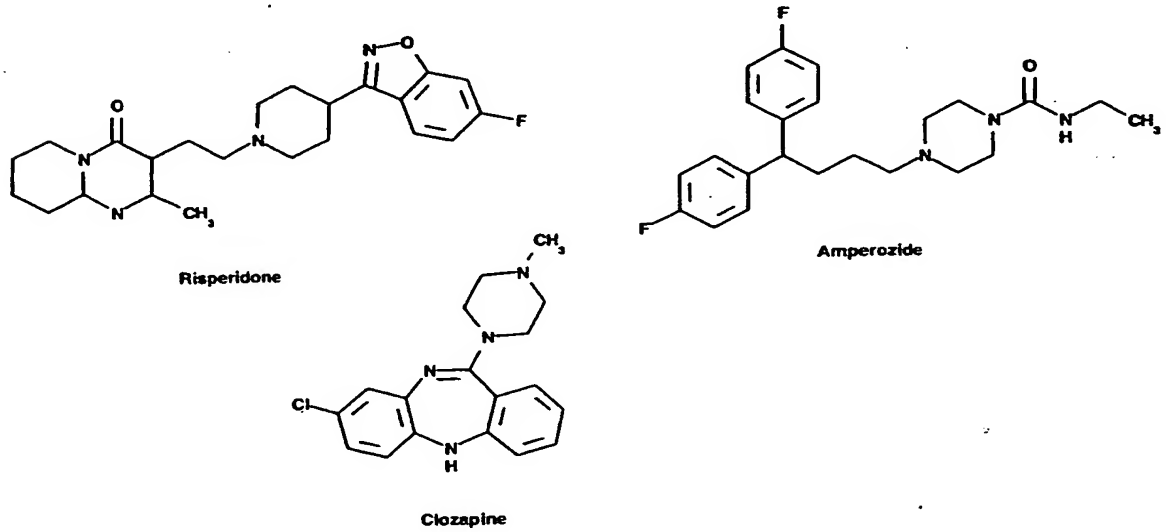


Figure 3: Antipsychotic agents

Autism

Autistic disorder is a syndrome originating in early childhood. It affects two to five children in every million, and is characterised by prominent distortions in social, linguistic and cognitive development. Pervasive lack of interest in others, and unresponsiveness to them, are essential features of the disorder.

Autistic children who develop spoken language often exhibit abnormal speech patterns including senseless or compulsive repetition of words heard (echolalia). Motor stereotypes such as hand flapping are common, as are self-abusive behaviours like head banging. Resistance to change is also characteristic. In the 1960s the syndrome was often described as early schizophrenia.

One prominent feature of autism is the presence of elevated plasma levels of 5-HT, which positively correlat with the cognitive, behavioural and motor deficits of subjects [388]. Studies of treatments designed to lower plasma 5-HT levels were therefore initiated. Early studies with fenfluramine, which is known to reduce brain 5-HT levels after chronic administration [389], reported dramatic effects in three autistic children [390]. However later studies have largely

found no effect of the drug on IQ or maladaptive behaviour and only a slight improvement in apparent developmental age [391]. The non-specific 5-HT antagonist, methysergide [16], was also without significant effect [392]. There is thus little evidence to support a role for 5-HT_{1C} receptor ligands in this disorder at the present time.

Table 6: Affinity of typical and atypical antipsychotic drugs for 5-HT_{1C} and 5-HT_2 receptors

Compound	pK_i 5-HT_{1C}	pK_i 5-HT_2	Selectivity for 5-HT_2 over 5-HT_{1C}	Class
Loxapine	9.4	8.7	4.7	Typical
Clozapine	8.1	8.3	1.4	Atypical
	8.1[a]	7.6[a]	0.3	
Tiosperone	8.0	10.2	153	Atypical
	7.6[a]	8.5[a]	7.9	
Fluperlapine	7.7	8.1	2.3	Atypical
Rilapine	7.6	9.1	29	Atypical
Chlorpromazine	7.6	8.7	13.5	Typical
	7.9[a]	8.1[a]	1.7	
Risperidone	7.5	9.7	160	Atypical
	7.5[a]	9.2[a]	49	
Setoperone	7.3[b]	8.6[b]	20	Atypical
Spiperone	6.0	9.4	2417	Typical
	6.0[a]	8.8[a]	631	
Amperozide	5.9	7.9	100	Atypical
Melperone	5.9	7.5	42	Atypical

All data from [380] except:
[a] Ref [379] [b] Ref [16]

Pain

5-HT_{1C} receptors have recently been identified in the spinal cord [393]. Iontophoretic administration of mCPP to dorsal horn nociceptive neurons located within the spinal cord is inhibitory [394]. Systemic administration of mCPP and TFMPP to spinal rats dose-dependently inhibited sensitivity to noxious stimuli which induce the ventroflexion withdrawal reflex [395]. This indicates a spinal or subspinal site of action. The pharmacology of these responses has not been investigated but 5-HT_{1C} receptor medication of antinociception was suggested by McKearney *et al.* [396]. In this study MK 212, mCPP and TFMPP all increase the shock intensity tolerated by monkeys. This effect was blocked by methysergide a non selective 5-HT_{1C} receptor antagonist (Table 1), but not by the selective 5-HT_2 receptor blockers ketanserin or pirenperone. Little human data exists, but, in contrast to the above, ritanserin was reported to increase subjective path thresholds [397]. This effect was modest however and might be related to the migraine prophylactic properties of the drug.

Priapism

MCPP, TFMPP or MK 212 administration causes penile erections in rats. MCPP-induced erections were antagonised by the 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin and ritanserin (Table 3, [231]) all of which have high affinity for the 5-HT_{1C} site [16]. The 50% inhibitory dose (ID_{50}) values of these drugs were higher than their equivalents against mCPP-induced hypophagia [66] but the rank order of potency was consistent in both paradigms. Ketanserin, the selective 5-HT_2 antagonist [16], also antagonised mCPP-induced penile erections but only at a relatively high dose [231] consistent with its weak affinity at the 5-HT_{1C} site [16] and its rank order of potency against mCPP-induced hypophagia [66]. The more selective 5-HT_2 receptor antagonist spiperone [16] was inactive [231]. Interestingly, the non-specific 5-HT_2/5-HT_{1C} agonist DOI (Table 3) only induced penile erections in the presence of specific 5-HT_2 receptor antagonists [231] suggesting an interaction between the two sites. MCPP also induced penile erection in rhesus monkeys which was blocked by metergoline [398]. The effect of mCPP may be mediated centrally as penile erections are seen in the rat after intraventricular administration of the 5-HT releasing agent fenfluramine [399], and the 5-HT precursor 5-hydroxytryptophan (5-HTP) is only effective when given with the peripheral decarboxylase inhibitor benserazide (Roche) [400].

In humans, priapism is a major disorder affecting ten million Americans [401]. Penile erection is caused by pooling of blood in the penile blood vessels. In priapism, prolonged stagnation of the pooled blood leads to a fall in oxygen content which increases its viscosity and results in fibrosis and impotence [402]. The condition is therefore considered a urological emergency. 30-50% of cases are drug induced, the most common agents being phenothiazines, butyrophenones, hypnotics (e.g. methaqualone), antihypertensives (eg phenoxybenzamine (SmithKline Beecham), prazosin (Pfizer), hydralazine), anticoagulants (heparin, warfarin) and miscellaneous agents such as ethanol, cannabis, phentolamine (Geigy) and testosterone [402]. Antidepressant therapy is also commonly associated with priapism, most notably with monoamine oxidase inhibitors such as phenelzine and the atypical antidepressant trazodone [402]. Since mCPP is a prominent metabolite of trazodone [56] this may explain its association with priapism, although this has not been reported as a consequence of mCPP administration to man [303]. MAOIs could act in a similar way by potentiating extracellular 5-HT. This may suggest a role for 5-HT_{1C} receptor antagonists in the prophylactic or acute treatment of this disorder, at least where caused by antidepressants.

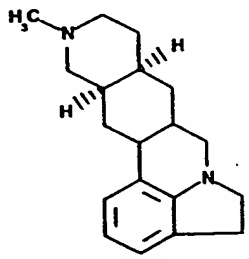
Altered intracranial pressure

The choroid plexus is the major site of formation of cerebral spinal fluid (CSF) in the brain [403,404]. Evidence suggests that 5-HT may control production of CSF, since administration of 5-HT and its precursor 5-HTP [405,406] are inhibitory. 5-HT may reach the choroid plexus from plasma, although concentrations are normally very low [407], or from mast cells found there [408,409]. Evidence also suggests direct serotonergic innervation. Thus moskowitz *et al.* [410] observed the presence of 5-HT that was sensitive to lesions of the raphe nuclei, the site of serotonergic neuronal cell bodies. Using a fluorescence technique that detected indoleamines, Napoleone *et al.* [411] reported that 5-HT neurons were located in the walls of the choroid blood vessels and were also sensitive to raphe cell body lesions. However not all studies have observed 5-HT innervation [412,413]. As has already been described (see above) the choroid plexus contains by far the highest concentration of 5-HT_{1C} receptors in any part of the body. It therefore seems likely that they mediate serotonergic control of CSF production as first suggested by Pazos *et al.* [6]. A recent study has shown that SCH 23390 (Schering Plough), a 5-HT_{1C} partial agonist [26,414] and dopamine D_1 antagonist [415], markedly

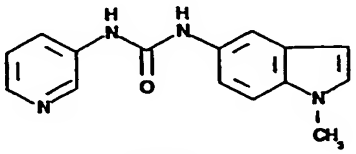
reduces CSF production in rats [416]. Since dopamine D_1 sites are not found in the choroid plexus [415] this effect is probably 5-HT_{1C} receptor mediated. These findings therefore suggest that 5-HT_{1C} receptor agonists may be of use in the treatment of patients with increased intracranial pressure such as those with mass lesions, head trauma, acute or hydrocephalus, or pseudotumour cerebri.

Conclusion

5-HT_{1C} receptor antagonists may have therapeutic applications in a number of areas. This possibility rests principally on the reported effects of the putative 5-HT_{1C} receptor agonist mCPP and of the non-specific 5-HT_2/5-HT_{1C} receptor antagonists ritanserin and mianserin as opposed to those of the selective 5-HT_2 receptor antagonist ketanserin. Unfortunately ketanserin is not entirely selective, possessing significant affinity for α_1 adrenergic receptors [250], a problem also seen with the newer selective 5-HT_2 receptor antagonist RP 62203 (Rhone Poulenc) [17]. Spiperone, which has proved of great value in defining 5-HT_{1C} functions *in vitro* due to its one thousand-fold selectivity for the 5-HT_2 site, is of little use *in vivo* because of its dopamine D_2 receptor antagonist properties. Similarly cisapride (Janssen) has one thousand-fold selectivity for the 5-HT_2 site but is also a potent 5-HT_3 antagonist and 5-HT_4 agonist [417]. Clarification of the therapeutic potential of 5-HT_{1C} receptor modulation should be considerably advanced by the recent development of selective 5-HT_{1C} receptor antagonists by both SmithKline Beecham [500] and Sandoz [501] (Figure 4) and the selective 5-HT_2 receptor antagonists RP 62203 [17] and MDL 101151 and its (+) isomer MDL 100907 which both have two hundred- to five hundred-fold selectivity for the 5-HT_2 site [418]. However it is also dependent on the pharmacological arguments advanced above, which are principally the result of animal data, being equally valid in humans. This cannot be taken for granted as mesulergine has fifty-fold lower affinity for the human than for the rat 5-HT_2 receptor. Thus in humans the drug would have selectivity for the 5-HT_{1C} site [21]. The probability that at least some of the above findings may be attributable to the action of drugs at the rat stomach fundus receptor (see section on receptor distribution), should it be found in human central tissue, cannot be excluded, despite preliminary evidence to the contrary [53,54]. In particular mCPP acts as a weak partial agonist of the rat stomach fundus [48,419] while most 5-HT_2/5-HT_{1C} receptor antagonists, but not specific 5-HT_2 receptor antagonists, are also antagonists of this site [48]. However current evidence strongly favours a therapeutic role for 5-HT_{1C} receptor ligands in at least some of the indications advanced in this review. Chronic treatment with selective 5-HT reuptake inhibitors is the current therapy of choice in many of these indications (OCD, alcoholism, depression, bulimia) and may become more widely used in others (panic disorder, obesity, migraine). Fluoxetine, the most widely studied drug in this class, is associated with significant side effects (insomnia, nausea, asthenia, tremor and sweating) [79] and may be associated with heightened risk of suicide in depressives [421-423] although these effects have not been reported for other 5-HT reuptake inhibitors. Furthermore, the reuptake inhibitors all require two or more weeks administration for effect. Should down regulation of 5-HT_{1C} receptors be their mode of action, the magnitude of this effect is unlikely to be as pronounced as that caused by an antagonist. Specific 5-HT_{1C} ligands may therefore offer advantages both in the speed of onset of action, efficacy, and side effect profile. Finally, it is conceivable that subtypes of the 5-HT_{1C} receptor may exist, although, with the exception of the rat stomach fundus receptor, there is no evidence of this at present. This might allow differentiation of the anxiogenic and other properties of 5-HT_{1C} receptor agonists facilitating their clinical use.



Sandoz



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SmithKline Beecham

Figure 4: Novel selective 5-HT_{1C} receptor antatagonists

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• = of interest •• = of considerable interest

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